CONTINUOUS INTRAVENOUS 2% LIDOCAINE INFUSION OR THORACIC EPIDURAL ANALGESIA FOR POSTOPERATIVE PAIN IN PATIENTS UNDERGOING ELECTIVE LAPAROSCOPIC ANTERIOR RESECTION AND LAPAROSCOPIC SIGMOID COLECTOMY : A COMPARISON

Dissertation submitted towards fulfilment of the rules and regulations of the Tamil Nadu Dr.M. G. R. Medical University for the M.D Branch X (Anaesthesiology) Examination to be held in May 2019

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled, "**CONTINUOUS INTRAVENOUS 2% LIDOCAINE INFUSION OR THORACIC EPIDURAL ANALGESIA FOR POSTOPERATIVE PAIN IN PATIENTS UNDERGOING ELECTIVE LAPAROSCOPIC ANTERIOR RESECTION AND LAPAROSCOPIC SIGMOID COLECTOMY: A COMPARISON"** is the bonafide work of Dr.Namitha.B.J, done towards the fulfilment of the requirements of The Tamil Nadu Dr.M.G.R Medical University, Chennai, for M.D Branch X (Anaesthesiology) Degree Examinations to be conducted in May 2019.

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This work was carried out under my guidance in the department

Dr. Tony Thomson Chandy

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PLAGIARISM CERTIFICATE

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CONTENTS

INTRODUCTION

Postoperative pain is a major barrier in recovery of patients undergoing laparoscopic surgeries, mostly in the first 24 hrs. Laparoscopic approach for colorectal resections has increased in acceptability because of less pain, bleeding and decreased complication rates when compared to open surgical approaches. The pain associated with laparoscopic surgeries is largely undermined and inadequately treated.

There are conflicting results with regard to lidocaine dose, duration and efficacy as analgesic even though it is part of ERAS (Enhanced Recovery After Surgery) guidelines for open abdominal surgeries. ERAS is an evidence - based fast track surgical protocol which has improved perioperative care, with shortened recovery time and early discharge.

Even though studies have demonstrated the superiority of epidural in open abdominal surgeries, its benefit in laparoscopic procedures is debatable. We aim to compare intravenous lidocaine infusion with thoracic epidural analgesia to determine the most efficient, cost-effective, safe, non opioid mode of analgesia for laparoscopic surgeries as the scope of lidocaine infusion in laparoscopic surgeries is still under debate.

Postoperative pain, by itself, does not reflect the overall quality of recovery of a patient. Hence, in addition to analgesia, we use the quality of recovery – 15 score to quantify postoperative recovery.

Integrating IV lidocaine with laparoscopic surgeries could potentially allow early discharge with an overall improvement in the quality of patient recovery.

AIMS AND OBJECTIVES

AIMS: The primary aim of our study is to find out which mode of postoperative analgesia (intravenous lidocaine infusion or thoracic epidural analgesia) will provide the best relief of early postoperative pain following elective laparoscopic colorectal surgeries.

OBJECTIVES:

1) To compare the effectiveness of intravenous Lidocaine infusion and Thoracic Epidural Analgesia (TEA) in attenuating acute postoperative pain in patients undergoing laparoscopic anterior/low anterior/ultra low anterior resection and sigmoid colectomy using Numeric Rating Scale (NRS).
2) To compare the effect of the said analgesic techniques on Quality of recovery using QoR 15 score, use of intravenous rescue analgesia (total opiods used) in the postoperative period, length of hospital stay and side effect at any point, when they occur (with IV Lidocaine - hypotension, bradycardia, syncope, seizures and with TEA - hypotension, epidural catheter misplacement, nerve root injury, urinary retention)

REVIEW OF LITERATURE

In 2012 about 1.4 million patients were diagnosed with colorectal cancers, of which about 7 lakh died from the disease. Colorectal cancers were the third most common cancer among males and second most in females.(1)

Fast track surgery or Enhanced Recovery after Abdominal Surgery (ERAS) in the area of colorectal surgery is a multimodal and a multi disciplinary approach with a goal towards decreasing postoperative complications and ensuring adequate postoperative analgesia and working towards early mobilization. This approach has decreased the complications by 20-30% and duration of hospital stay from 8-12 days to 3-4 days(2)

Laparoscopic surgery for colorectal cancer has increased in acceptability because of the relatively less pain and decreased risk of complications that are associated with open colorectal resections like surgical site infection, anastomotic leakage, intra – abdominal abscess, ileus and bleeding (3). Laparoscopic procedures have been shown to attenuate the stress response following colorectal resections by decreased serum epinephrine and insulin levels(4). Laparoscopic surgeries also have some beneficial effect on the return of bowel function and hence it may help in early discharge of the patient. However, nociceptic input (45%) remains comparable between open and laparoscopic surgeries in the first four hours and laparoscopic surgeries. Often laparoscopic surgeries require more analgesia during this period (5,6)

Epidural is one of the analgesic modality used in laparoscopic colorectal surgeries. It has been widely popular as part of Enhance Recovery After Surgery (ERAS)

protocols. Thoracic epidural has been associated with early return of bowel function attributed to decreased use of opioids to treat surgical pain, blockade of sympathetic hyperactivity that is mediated by nociceptive afferents via spinal arc that is responsible for bowel hypomotility and diminished propulsive effects (7,8). Both nociceptive afferent innervations and sympathetic efferent nerves are known to cause ileus. Another probable mechanism is the systemic absorption of local anaesthetics from the epidural space which might improve colonic blood flow and effect early return of bowel function (9) . TEA also helps to decrease the postoperative pulmonary complications in high risk pulmonary patients(10). However, the use of epidurals for intraoperative and postoperative analgesia were the recommendations of the elective open surgery era and have been carried forward to use for laparoscopic surgeries today. Though epidural has benefits in post operative analgesia and the duration of postoperative ileus, it does have some adverse effects such as bleeding complications (epidural hematoma), infection within the spinal canal causing meningitis, epidural abscess (11), pruritus, urinary retention, arterial hypotension, technical challenges and the requirement of a skilled anaesthetist. While it did not make a significant influence on length of hospital stay(12) , small studies have shown surprising lack of benefit of epidural in preventing ileus and reducing the duration of convalescence(13) even though there was good analgesia with epidurals. Therefore the role of epidural analgesia in laparoscopic surgery is unclear.

Various methods of pain control are being explored such as regional anaesthetic techniques which include nerve blocks, local wound infiltrations, epidural analgesia,

systemically administered analgesics like paracetamol, NSAIDS, opioids, ketamine, ketorolac and other adjuncts.

An additional method of acute pain control is the use of perioperative intravenous lidocaine. There is some evidence that intravenous lidocaine infusion may offer better postoperative pain relief. An added advantage was decreased hospital stay and improvement of postoperative bowel function in various laparoscopic surgeries like laparoscopic nephrectomy (14) , gynaecological surgeries (15), prostatectomy and major abdominal and colorectal surgeries (9)

Systemic administration of lidocaine has analgesic, antihyperalgesic (16) and anti-inflammatory effects (7,17,18). Early functional recovery of bowel is probably due to reduction of postoperative opioid consumption (19–21), anti-inflammatory property (7) of lidocaine and direct inhibition of sympathetic mesenteric plexus.

Weibel et al (22) conducted a systematic review, with trial sequential analysis assessing the efficacy and safety of intravenous lidocaine administration for post operative analgesia and recovery after surgery. Lidocaine reduced postoperative pain scores (0-10cm, 0 – 100 mm VAS, Numeric Rating Scale, Verbal Rating Scale) at 1-4 hours and at 24 hours after surgery. The best benefit of lidocaine infusion on the duration of pain relief , opioid consumption and postoperative nausea and vomiting (PONV) was found to be in laparoscopic abdominal surgery followed by open abdominal surgery. The results were clinically pertinent in terms of enhanced analgesic effect particularly in the early (1 – 4 hours) postoperative period. The study

also reported no major side effects associated with perioperative continuous lidocaine infusion in clinically used dosage (1.5mg/kg bolus and 2 mg/kg/hour infusion). This was based on the review of 45 small randomized control trials and there was no methodical screening of the adverse effects related to toxicity. However, the opioid requirements, postoperative nausea and vomiting, length of hospital stay and surgical complications were not ascertained due to clinical variability, difference in methodology and small sample size of the studies. There was also a limited evidence of positive effects on gastrointestinal recovery.

A Cochrane review by Kranke et al (23) looked at the role of intravenous lidocaine in comparison with other known postoperative analgesia methods. Subgroup analysis comparing thoracic epidural analgesia with intravenous lidocaine did not find any difference between the arms with regards to postoperative pain, return of bowel function and length of hospital stay. There were only two studies from which they made the comparison. Wongyingsinn et al (24) included 60 patients who were scheduled to undergo elective laparoscopic colorectal surgery whereas Swenson et al (25) studied 42 patients undergoing open abdominal surgery. Both the studies did not look at patient satisfaction. The review did not adequately address the incidence of adverse effects related to lidocaine infusion (such as arrhythmias, signs and symptoms of lidocaine toxicity and death).

LIDOCAINE

PHYSICAL PROPERTIES:

In its crystalline, dry anhydrous form, lidocaine is slightly yellow or white powder with a characteristic odour. The dissolved hydrochloride salt is colourless (26). It is stable at room temperature of around 25 degree celsius (77 degree Fahrenheit) and it should be protected from sunlight. Plain preparations are sterilised by autoclaving, even upto two times. pH is adjusted to 5.0 to 7.0 by mixing either sodium hydroxide, sodium chloride or hydrochloric acid (27). It is available as preparations with or without adrenaline. Lidocaine crystals have a melting point of 70° C and a boiling point of 170° C.

CHEMICAL PROPERTIES :

The molecular weight of lidocaine is 234.343 g/mol and its molecular formula is $C_{14}H_{22}N_2O$. The pH is reduced to 3.3 - 5.5 by adding adrenaline. It has a pKa of 7.86 at 25 degree Celsius. The Oil/Water Coefficient is 2.9.

PHARMACOLOGIC CLASSIFICATION :

Lidocaine is a local anaesthetic which belongs to the amino - amide group. It is also included under Class 1b anti - arrhythmic agents as per Vaughn Williams classification of anti - arrhythmic drugs.

STRUCTURE:

A local anaesthetic , in general , is made up of an aromatic group - an intermediate chain – amide group. Lidocaine has the aromatic portion linked by the amide intermediate bond to a tertiary ethylamine portion.

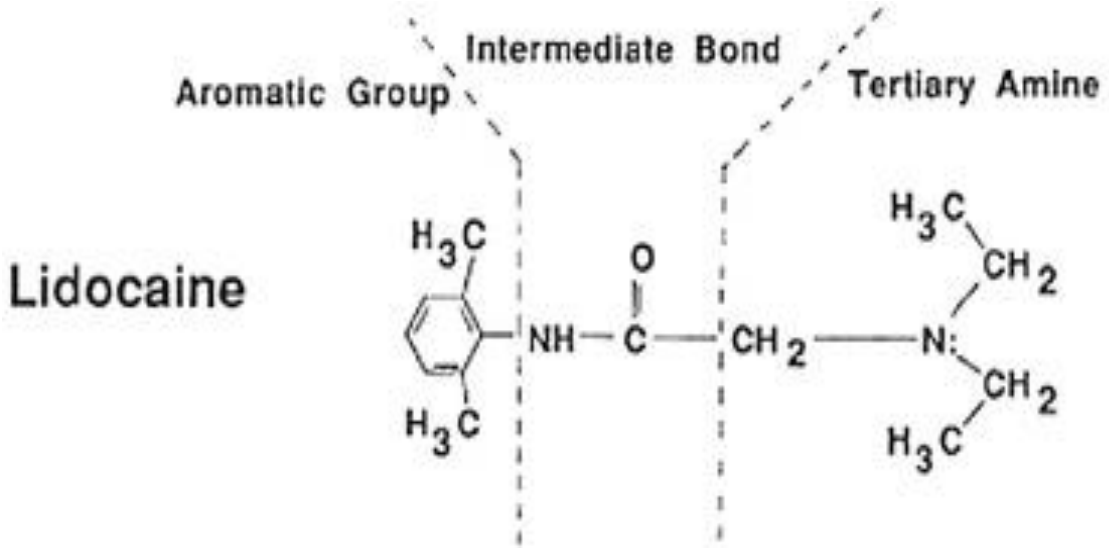


Figure 1: The molecular structure of lidocaine. The aromatic group provides the lipophilicity and as the tertiary amine gets protonated it confers hydrophilicity (28)

PHARMACOLOGY

Lidocaine was first discovered in the early 1940's by two Swedish chemists Nils Lofgren and Bengt Lundqvist in the Institute of Chemistry at Stockholm University, Stockholm (29). Clinical investigations conducted by Dr.Torsten Gordh, the first anaesthetist in Sweden, from 1944 to 1947, lead to its widespread use in surgery. He showed that lidocaine had a quicker onset and a longer duration of action in comparison to procaine, which was the most commonly used local anaesthetic in those

days. Procaine was only available in powdered form and had to be carefully diluted with adrenaline to prolong its duration of action. Gordh tested lidocaine by raising intradermal wheals and subcutaneous injections and using needle point to determine sensory loss. The effect of procaine was found in the wheal for only17 minutes , but on comparison, lidocaine lasted for almost 70 minutes. He also observed that it was associated with lesser side effects and was more steady and durable when used with adrenaline as the preservative. The discovery of lidocaine transformed the world of regional anaesthesia almost overnight (29).

Lofgren and Lundqvist originally named the compound LL30 after their own names. Later , due to Gordh's connections with pharmaceutical companies, specifically Astra AB , LL30 became widely popular under its current brand name , Xylocaine (29,30). The first article on lidocaine was published in Swedish in 1948 by Goldberg , in correspondence with Gordh. The next year, Gordh himself wrote an article, *'Xylocain – A New Local Analgesic*' (31) in the international journal *Anaesthesia.*

Figure 2: LL30 was initially distributed in glass syringes which were packed in blue colored rectangular cardboard boxes (32)

Soon, lidocaine was used in a wide variety of surgeries like thyroids, hernia, thoracotomies, eye surgeries, nerve block (29).

It also found its way into the subarachnoid space after Lundqvist managed to accomplish a spinal block on himself successfully using a mirror (32).

Lidocaine was later added to the Essential Medicines list by WHO. The WHO Model List of Essential Medicines is a set of medications that satisfy the primary healthcare needs of the community and for that reason, these drugs should be available at all times, in appropriate quantity, dosage forms and at an affordable price so that the country's core population can deal with the priority health issues (33). The list is updated every 2 years.

The IUPAC NAME of lidocaine is 2-(diethylamino)-N(2,6dimethylphenyl)acetamide.

Xylocain , Lidocaine , Xylocard are the currently used trade names of Lidocaine.

SYNTHESIS

Lidocaine is a sterile isotonic solution available as Lidocaine Hydrochloride. It is synthesized when 2,6-dimethylaniline interacts with chloroacetyl chloride in sodium acetate and glacial acetic acid. The resulting compound chloroacetyl-2,6-dimethylanilide is boiled in benzene along with diethylamine. This reaction produces Lidocaine hydrochloride which crystallizes in its hydrous form with one molecule of water which is removed by careful drying to give anhydrous Lidocaine hydrochloride.

DOSAGE:

Animal studies are used to determine the maximum doses. The volume and concentration used in a patient also depends on the physical condition of the patient. Patients with liver disease, cardiac compromise, paediatric and geriatric patients need a careful dose reduction to avoid toxic side effects, which have a direct correlation with the total dose of lidocaine used. Hence higher dose and concentrations should be used cautiously.

The maximum total dose of Lidocaine is 300 (4.5 mg/kg) – 500 mg (< 7 mg/kg, with 1 : 200000 epinephrine) (34) in a 70 kg man. Plasma concentration of lidocaine above which toxic effects are evident is found to be > 5mcg/ml (35) . For central nervous system toxicity, the ED 50 of intravenous lidocaine is around 19.5 mg/kg (95%CI - 17.7-21.3 mg/kg) and for ECG changes to be evident, the dose is about 21 mg/kg (95%CI: 19.0-23.4 mg/kg) [71] or as reported by Gianelly, a plasma level of 9 – 10 mcg/mL which corresponds to a dose of 5mg/min infusion in a 70 kg patient (36). Clinically effective analgesic dose of lidocaine that can be given intravenously is 1.5 – 3 mg/kg/hr (37). A bolus of 1 – 2 mg/kg/hr followed by an infusion at 1.5 mg/kg/hr translates to a plasma level of 2 mcg/ml (38). Although there is a theoretical risk of accumulation of lidocaine and toxicity with continuous infusion, Kaba et al established that a 24 hour infusion of 2mg/kg/hr dose did not cause any significant side effects and plasma levels remained below 5mcg/ml (39).

PHARMACOKINETICS:

The pharmacokinetic properties of lidocaine were first evaluated by Friden (40) in 1965 and later by Beckett (41) , who studied the plasma half life after a 50 – 100 mg intravenous bolus dose. A couple of years later, Gianelly (36) studied about the peak plasma half life, therapeutic and toxic doses in patients with myocardial infarction or known coronary heart disease.

ABSORPTION:

The absorption of local anaesthetics depend on various factors like the site of injection, local tissue perfusion, the dose , concentration and volume of the anaesthetic, presence or absence of a vasoconstrictor agent (eg. Epinephrine) and the pharmacological properties of the drug. It is found that the highest concentration of local anaesthetic in blood is found after intercostal nerve block (approximately 1.5μg/mL for every 100 mg) (27), followed by its administration into the caudal epidural space > lumbar epidural space > brachial plexus and least in subcutaneous injections (approximately 0.5 μg/mL per 100 mg) (27,42). The addition of epinephrine (1 : 200000) significantly prolongs the absorption of the drug and reduces the concentration in the plasma.

Lidocaine is entirely absorbed after parenteral administration. Oral administration is associated with unpredictable first pass metabolism and hence a corresponding higher dose is needed. About 1-5 minutes is needed for onset of action after local infiltration into the skin and about 5 – 15 minutes after perineural infiltration used for peripheral nerve blockade and other routes of administration (27). About 20 – 30 minutes is

required for lidocaine to reach its peak plasma levels irrespective of the site of administration. However, an initial intravenous bolus causes immediate peak levels in the plasma (36,43)

DISTRIBUTION:

The pattern of systemic distribution of Lidocaine is explained by the two compartment model (44,45). The concentration of local anaesthetic drugs varies in different tissues and is proportional to the amount of tissue perfusion. After the intravenous administration, initially there is a significant drop in the plasma concentration because of its extraction by the lungs. But soon, an equilibrium is established between the pulmonary tissue and blood, which results in an increase in the blood concentration of lidocaine. This is followed by a decrease in plasma levels due to *redistribution* into the well vascularised tissues like brain, heart, kidneys and liver. As a result, there is a decreased concentration in poorly perfused organs like adipose tissue, skin and muscles. Local anaesthetics accumulate in vascularised tissues and the concentration is lesser in organs with low vascularity.

The volume of distribution after intravenous administration is 0.6 – 4.5 L/kg (46). At plasma levels of 1 – 4 mcg/mL, the protein binding is about 60 - 80 % which has an inverse relation with its plasma concentration. The fraction of the plasma bound drug also depends on the amount of $alpha_1$ acid glycoprotein. Depending on the pH of the surrounding medium, lidocaine can exist in either the ionised or unionised form. It is a weak base, and hence exists in the unionised form in basic environment, which means that it can easily travel across the cell membrane.

The mechanism of transfer across placenta and the blood – brain barrier is simple diffusion. The total plasma concentration of lignocaine will be higher in the mother in comparison to the fetus since the protein binding is higher, although the concentration of free drug is same in both (27)

METABOLISM AND CLEARANCE :

Lidocaine is metabolised in the liver which correlates with its concentration in the plasma in a linear fashion. This continues until the drug is excreted from the body. When lidocaine is administered as an infusion, then a steady state must be established in the plasma. This is achieved when the sum of the drug metabolised and redistributed to the poorly perfused compartment is equal to the dose administered at that time.

Lidocaine is mainly metabolised in the hepatic cytochrome p-450 system. Only about 10% is eliminated unchanged in the urine. The remaining 90% of the drug is metabolized in the liver into its active metabolites Monoethylglycine xylidide (MEGX) via cytochrome p450 3A4 mediated N-dealkylation and glycine xylidide (GX) via hydrolysis of lidocaine (27,43). These metabolites have similar pharmacological action but are less potent when compared to lidocaine.

Most of the antiarrhythmic function of lidocaine can be attributed to its metabolite – MEGX, whereas GX has only about 10% of the activity. MEGX also has longer half life and hence has continued action even after discontinuation of lidocaine. Accumulation MEGX is also associated with epileptic activity after prolonged infusion even in therapeutic non toxic doses. MEGX and GX are further metabolised

to form xylidine and 4-hydroxyxylidine which get eliminated by the kidneys in urine at a rate of 10-20 ml/min/Kg. The total plasma clearance is 0.95 L/min.

The metabolism is proportional to the hepatic blood flow with an estimated hepatic extraction ratio of 0.65, hence careful dose reduction is needed in decompensated liver disease, congestive heart failure and acute myocardial infarction which are states of fluid retention. Conditions affecting hepatic perfusion like pregnancy and anaesthesia can prolong the half life and can cause reduction in lidocaine clearance significantly. The elimination half-life is 90-120 minutes (47)

Following an intravenous bolus dose, the onset of action is 45 to 90 seconds and the duration of action is 10 to 20 minutes, the redistribution half-life around 7-30 minutes. The elimination half life of intravenous infusion of < 12 hr duration is about 100 minutes and it follows linear pharmacokinetics, however the elimination half life following an infusion of > 12 hours is approximately 4 hours, and the pharmacokinetics becomes time dependant or non – linear.

PHARMACOKINETICS OF INFUSION:

The goal of any drug infusion is to attain a steady state level, exclusive of any toxic side effects. In the case of lidocaine, we need a plasma concentration between 0.5 – 5mcg/ml for clinically significant analgesic effect (48). Administration of an intravenous lidocaine bolus prior to lidocaine infusion achieves therapeutic levels in the blood rapidly. Hsu et al established that lidocaine infusion doses should be calculated according to the body weight, and the dose should be reduced after 24 hours to prevent toxic effects (49).

PHARMACODYNAMICS

SITE OF ACTION :

1) NERVE FIBRES:

Lidocaine binds to the alpha subunit of the voltage gated sodium channels in all excitable tissues including skeletal, smooth and cardiac muscle fibres.

Lidocaine also facilitates better relaxation by acting on the sodium channels present on the vascular smooth muscle cells. Thus it can potentially cause some amount of arterial vasodilation

Fiber Classification	Diameter (μm)	Myelination	Conduction Velocity (m/s)	Anatomical Location	Function	Local Anesthetic Susceptibility
Aα	6–22	Yes	30–120	Efferent to muscles	Motor	++
Aβ	6–22	Yes	30–120	Afferent from skin and joints	Touch and proprioception	++
Aγ	3–6	Yes	15–35	Efferent to muscle spindles	Muscle tone	++++
Aδ	1–4	Yes	5–25	Afferent sensory	Distinct, well-localized (fast) pain, cold temperature, touch	+++
B	<3	Yes	3–15	Preganglionic sympathetic	Autonomic	++
C	0.3–1.3	No	0.7–1.3	Afferent sensory, postganglionic sympathetic	Autonomic, warm temperature, touch, and diffuse (slow) pain	+

+ (least susceptible), ++, +++, ++++ (most susceptible) to conduction blockade.

Figure 3: Level of susceptibility of different types of nerve fibres to lidocaine induced blockade (50).

Intravenous lidocaine acts on the sodium channels of the central and peripheral nervous system, from the intracellular part of the cell membrane. Most of the nociceptive input from the peripheral nerves and the sympathetic nervous system is mediated by the voltage – gated sodium channels (51). These channels are also responsible for the hyperexcitability of the damaged peripheral nerves and are hypothesized to be the cause of neuropathic pain (38,51,52). Thus blockade of the ascending nociceptive pathway facilitates pain relief.

The origin of pain is either visceral or somatic. Contrary to the general perception, visceral pain differs from somatic pain. Somatic pain originates from pain receptors in the skeletal system and is well localized in nature (53). Visceral pain is carried by the A – delta and C – fibres, which trigger pain centres in the central nervous system. The A- beta fibres are responsible for the exaggerated pain response to tactile stimulation when they carry nocicceptive inputs from the injured nerve endings (54). Visceral pain originates from the nociceptors present in cardiovascular, respiratory, gastrointestinal and genitourinary systems (53). It is often diffuse in nature and is responsible for referred pain either adjacent to or remote to the tissue of origin, like referred pain from the gut to the body surface. For example, a full bladder/ rectum, inflamed gut like in irritable blowel disease / inflammatory bowel disease or inflammation post surgical stress can cause severe pain and discomfort to the patient leading to states of hyperalgesia.

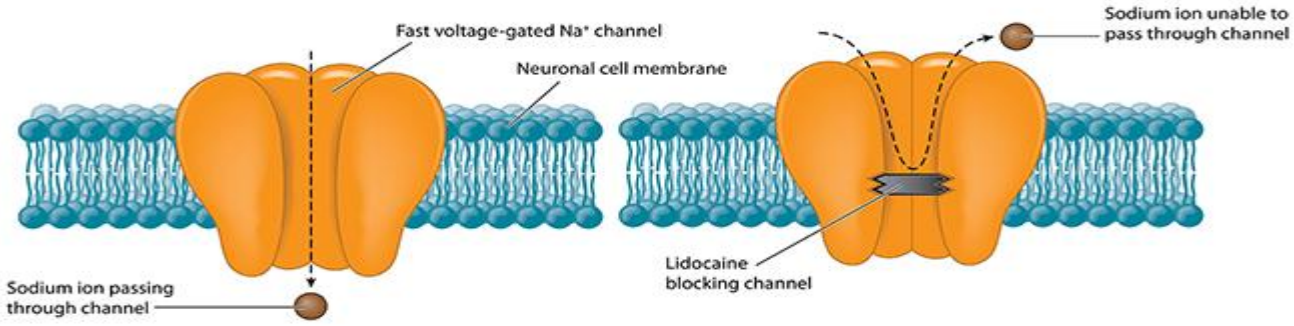


Figure 4 : Lidocaine blocking the sodium channel on the lipid bilayer on plasma membrane (55)

THE SODIUM CHANNEL:

The channel exists in the resting state by and large, where any voltage fluctuations that occur during depolarisation cause conformational changes which will activate the channel and let sodium ions to pass through. The channel then exists in a state of inactivation, which momentarily stops the passage of ions and then finally reverts back to the resting state.

Lidocaine binds to the sodium channel at the alpha subunit. There are more than 8 isomers to the α-subunit with variable sensitivities to lidocaine. The drug reaches the sodium channel through the phospholipid bilayer cell membrane, directly via hydrophilic pathway, the faster acting than the hydrophobic pathway which has a relatively slower pathway (42).

Due to favourable structural conformation, lidocaine has a better affinity to the sodium channel during the open or inactivated states. This is essentially the basis of use and phase dependant block. Lidocaine activity is principally by the cationic protonated form which enters the cell and reaches the channel during channel depolarization. The slower hydrophilic pathway allows the lidocaine molecule to enter the cell through the lipid bilayer directly and get protonated there. It then binds to the sodium channel. Once bound, the resting membrane potential does not change significantly, but action potential conduction eventually decreases until it is completely abolished at therapeutic concentration.

EFFECTS OF INTRAVENOUS LIDOCAINE

ANALGESIA (23,43,56–58) : The mechanisms postulated to explain the analgesic action of lidocaine are multifactorial. The central action is the blockade of potassium currents and sodium channels on nerve membrane (33), muscarinic receptor antagonistic action, glycine inhibitor, reduction in excitatory amino acids, thromboxane - A2, neurokinins, and release of endogenous opioid peptides, ATP-adenosine triphosphate (38). Lidocaine also has anti - hyperalgesic effect in patients on opioid medications. These patients have a paradoxical increased sensitivity to noxious stimuli and thus have increased requirements of analgesia and increased pain. Hyperalgesia is attributed to changes in the activity of NMDA and glutamate transporter system (59)

WOUND HEALING EFFECT (17,39,60–63) : Due to retardation of mucopolysaccharide and collagen synthesis, inhibition of oxygen free radical production, inflammatory cytokines, vascular permeability and edema formation.

ANTI – THROMBOTIC EFFECTS (64): This is attributed to inhibition of thrombus formation by reducing platelet aggregation via blockade of calcium influx and mobilization of intracellular calcium stores.

ANTI-INFLAMMATORY EFFECT AND IMMUNE CELL MEDIATOR INHIBITION: (17,43,62,65–67): By blockade of the sodium channels, and inhibiting G-protein coupled receptors and N-Methyl-D-Aspartate receptors in ascending pain pathways (68), lidocaine acts as an anti – inflammatory agent. It acts on the potassium channels present on the mitochondria, which are sensitive to Adenosine Tri – Phosphate (ATP) (69–71). Lidocaine also inhibits monocytes, reduces the production of interleukin 1α, β and 8, tumour necrosis factor. It inhibits neutrophils, prostaglandins, thromboxane, leukotrienes, lysosomal enzymes and free radicals. It is also known to reduce histamine release by inhibiting mast cell activity.

BACTERICIDAL EFFECTS (43,72–75), **ANTI - VIRAL EFFECTS** (17) **AND ANTI - FUNGAL EFFECTS** (17,74): Lidocaine is found to inhibit the growth of Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Haemophilus influenza, Mycobacterium tuberculosis, Herpes simplex virus and Candida albicans

PROTECTIVE EFFECTS AGAINST : (58,60,61,64,68,74–77): ARDS, severe sepsis, ischemia-reperfusion injuries, cardiac ischemia, interstitial cystitis, ulcerative proctitis, ulcerative colitis and thermal injuries

EARLY RETURN OF BOWEL FUNCTION AFTER MAJOR SURGERIES:

(15,23,39,56,57,78,79) : Attributed to the opioid sparing action and inhibition of sympathetic outflow from the gut.

POST-OPERATIVE NAUSEA & VOMITING: Lidocaine has opioid sparing action which prevents PONV.

REDUCED HEMODYNAMIC VARIATION: Blockade of sodium channels in the smooth muscles and sympathetic nervous system supplying the cardiovascular system. This in addition to blockade of the afferent pain and sensory fibres provide superior hemodynamics particularly during intubation, creation of pneumoperitoneum, surgical stimulus and extubation.

DECREASES AIRWAY HYPERACTIVITY IN ASTHMA: (80–82) Intravenous lidocaine was reported to reduce the histamine release and thus bronchoconstriction.

TREATMENT OF INTRACTABLE HICCUPS: (83–87) Lidocaine has anaesthetic effect on the irritated nerve endings when given in the nebulized form, thus treating hiccups.

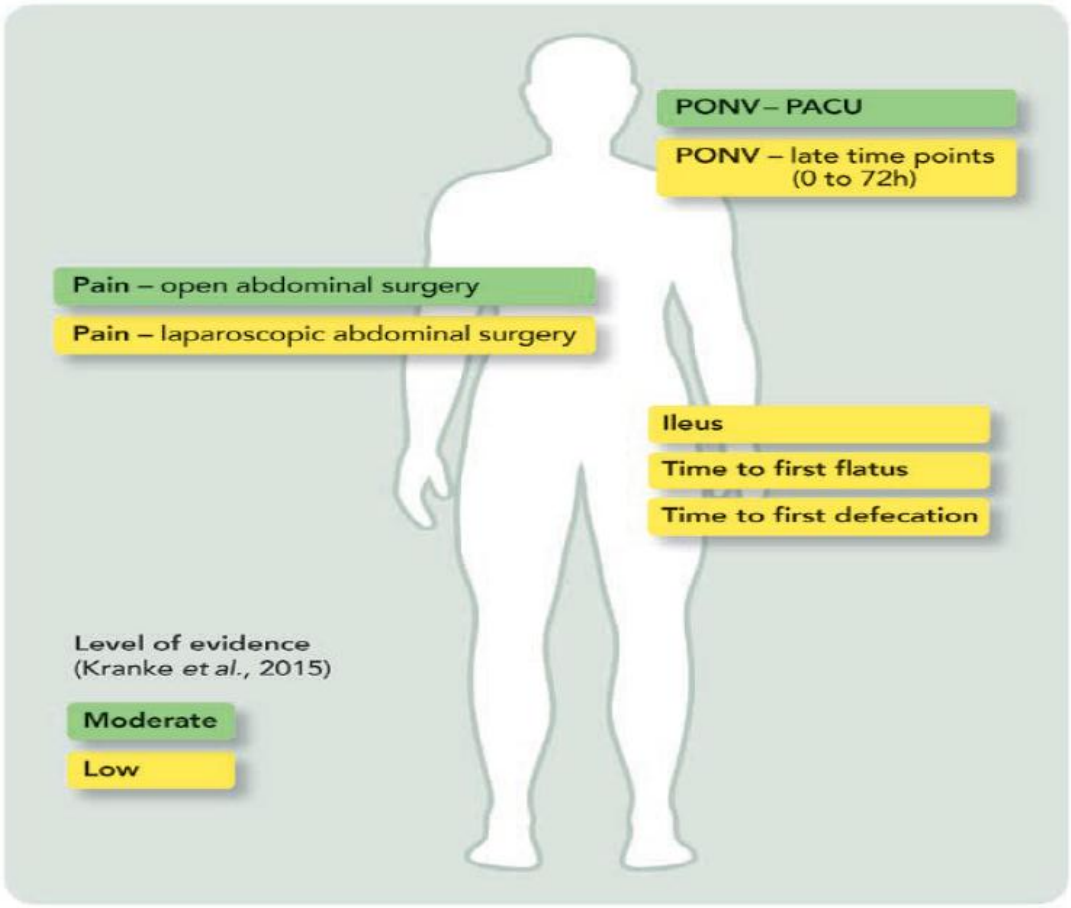


Figure 5: Benefits of lidocaine in abdominal surgeries (23)

ADVERSE EFFECTS OF LIDOCAINE

The side effects (88–90) are proportional to the serum lidocaine level, site of administration, as well as on patients' overall status with regard to age, clinical conditions, pregnancy. When serum levels are below 5 mcg/mL there is analgesic effect and inhibition of cortical motor neurons, and hence its anticonvulsant activity can be explained (91). Beyond 5 mcg/ml, adverse effects are directly related to the blood concentrations (92).

Mild toxicity occurs at serum levels of 3- 8 mcg/ml and manifests as numbness and tingling in the fingers and toes, perioral numbness and paresthesia, metallic taste in the mouth, tinnitus, light-headedness and dizziness. Moderate toxicity is seen at serum levels of 8-12 mcg/ml and can cause nausea and vomiting, dizziness, decreased hearing, tremors, changes in blood pressure and pulse. Severe side effects are observed at serum levels greater than 12 mcg/ml which leads to severe CNS and cardiovascular abnormalities. It causes drowsiness confusion, muscle twitching, convulsions, loss of consciousness, cardiac arrhythmias and cardiac arrest.

THORACIC EPIDURAL ANALGESIA

20th century saw the rise of epidural analgesia for pain management. Upto 1920, only sacral space via sacral hiatus was accessible for administration of drugs, pioneered by Dr.Jean Anthanese Sicard, a urologist from France. He described the use of cocaine, among other compounds (like potassium bromide, potassium iodide, etc) to treat a number of conditions including sciatica. However, it was not possible to reproduce satisfactory results when a French surgeon Fernand Cathelin injected cocaine in sacral hiatus in 1901 (93). However, in 1921, a Spanish military surgeon, Fidel Page , for the first time, described the injection of anaesthetic agents into the lumbar and thoracic epidural spaces for analgesia. This marked a milestone in the field of epidural anaesthesia. The technique involves injecting local anaesthetic agents into the continuous space present between the duramater and the walls of spinal canal. Based on the volume and dose injected, analgesia maybe limited to lower dermatomes (caudal block) or may extend up to block higher segmental dermatomes involving lumbar and thoracic areas (lumbar and thoracic epidural block respectively). Page's technique was called 'metameric anaesthesia' (94). He used 20 ml of 2% novocain in most of his studies. He played a pivotal role in describing the correct technique, anatomy, pharmacology , indications and adverse effects of epidural anaesthesia. Later in 1949, continuous epidural anaesthesia by introducing catheters into the epidural space was introduced and was extensively applied for surgery and obstetrics.

In modern times, thoracic epidural analgesia (TEA) has been extensively used for intraoperative and postoperative analgesia in major abdominal surgeries (10,95,96), both open and laparoscopic.

EFFECTS OF TEA:

Sympathetic blockade (97,98) caused by TEA avoids injury associated due to sympathetic activation associated with surgical stress like increases in catecholamines, immune response against host and activation of coagulation system. There might be a reduction in pain and thus decreased postoperative pulmonary atelectasis in patients undergoing CABG, reduced incidence of pneumonia and improved oxygenation in the postoperative period (10,99,100). Carli et al (97) showed that TEA might improve regional blood flow to the heart and thus affect myocardial oxygen consumption. There are also reports of reduced cardiac dysrhythmias after cardiac surgeries (101). There is some evidence about the favourable effect of TEA on intestinal perfusion (102) provided hemodynamics is maintained intraoperatively using vasopressors (103). TEA is associated with improved postoperative intestinal motility in major open abdominal surgeries (12,104,105). Majority of the studies compared epidural (with or without epidural opioid) with systemic opioids for postoperative pain control. Only two studies compared TEA with systemic lidocaine in the assessment of early bowel motility, one study showed TEA was better than lidocaine infusion (7) whereas the other recent study has shown no difference in both groups (25). TEA is known to significantly lower the rates of anastomotic compromise in emergency laparotomies (106) and gastrointestinal surgeries (107,108). In 2001, a meta-analysis of 12 clinical

trials compared epidural and systemic analgesia relating to anastomotic leaks, showed neither improved nor worsened anastomotic outcomes (109).

There are speculations about the benefit of TEA in reducing tumor recurrence (110) probably due to improved immune responses caused by the attenuation of stress induced tumor spread or by the opioid sparing effect. Morphine, in particular, has, time and again, been associated with tumor spread in colon and breast cancers an animal models (111–114).

DISADVANTAGES OF TEA:

Caution must be exercised so as to avoid traumatic puncture and adequate history with regards to the use of anticoagulation and renal impairment must be taken as epidural techniques can result is epidural haematoma formation. On the other hand, it should be kept in mind that withdrawal of anticoagulation for the purpose of TEA may increase the risk of thromboembolism. Since TEA is an invasive procedure, there is a potential for infective complication (epidural abscess, spinal cord compression, meningitis, etc.) to occur. There is also a risk of dense motor block, inadequate level of analgesia, catheter misplacement and urinary retention, all of which can increase patient discomfort. There needs to be a dedicated team of trained staff to recognize neurological complications and who are aware of the epidural drug doses and infusion regimen in the surgical wards, which may be more expensive than other modes of analgesia. Levy et al (13) studied the effect of epidural , spinal analgesia and PCA on quality of life using parameters like return of bowel function, length of hospital stay and bowel function among patients undergoing laparoscopic surgeries. They reported

better pain scores in the epidural group, however the quality of life was much worse with epidural as compared to spinal analgesia or PCA.

PCA - CADD PUMP

CADD (Continuous Ambulatory Delivery Device) is a drug delivery technology that is used as a type of patient controlled analgesia (PCA). It is used to deliver a fixed dose of opioids on demand with or without a background infusion. It consists of a programmable syringe pump which can be effortlessly used by the patient to control the drug delivery both in the hospital and outpatient settings.

Figure 6: CADD-Legacy PCA pump used in the study, showing the display screen, keypad and the cassette; manufactured by Smiths Medical.

PCA was first described in 1968 and was introduced for general use in the 1980's.

Modalities: PCA is being used in various modes like intravenous, intra-arterial, subcutaneous, intraperitoneal, peripheral nerve catheters, epidural space, or subarachnoid space infusion. Administration of analgesics via epidural/ subarachnoid space is limited to use with indwelling catheters meant for short-term or long term drug delivery.

Delivery methods: The device is intended for treatments that require a continuous analgesic infusion, patient controlled demand doses or both (such as patient controlled analgesia). There are three methods of delivery that can be incorporated either alone or in combination -

1. Continuous rate – (in mg/hr, mL/hr, mcg/hr depending on the units with a maximum rate of 50 mL/hr) – refers to continuous administration at a predetermined rate, which can be supplemented by intermittent boluses when required.
2. Demand Dose – refers to the fixed amount of drug delivered when the patient presses.
3. Clinician bolus – when the pump allows the clinician to give a bolus/loading dose at any point irrespective of the lockout settings.

The main advantage of PCA is that patients have direct 'control' over the drug delivery and for this reason there is immediate relief of pain and associated with lesser anxiety among staff and family members. There have been reports of higher patient

satisfaction as compared to frequent intramuscular medications. It is a safer mode of analgesia as only fixed dose of the drug can be given at a fixed interval. Safety is increased by 'lockout' interval, i.e., even if the patient presses the button, the PCA will not deliver the dose during the lockout time (usually 5 – 15 minutes). It is important to educate the patient both preoperatively and postoperatively regarding the use of PCA.

Features: The PCA pump incorporates the following programmable settings:

1. Loading dose – the dose used to adjust the opioid so it reaches its 'Minimum Effective Analgesic Concentration' (MEAC) i.e., the lowest concentration required to relieve pain.
2. Bolus dose – the dose delivered when the patient presses the handheld remote button
3. Lockout time – the time interval during which no dose is delivered even if the patient presses the remote. It is meant to reduce the risk of overdose and allows the drug to reach its peak effect concentration before the next dose.
4. Background infusion – refers to the continuous infusion that is sometimes necessary after major surgeries, in cancer or burns related pain ; maybe associated with dose - related side effects

Drugs: Morphine is the analgesic of choice. The other drugs used are Hydromorphone, Meperidine (in patients with allergy to both hydromorphone and morphine), Fentanyl.

Disadvantages: Safety is compromised in patients who are unable to understand the concept of PCA. Careful titration is required in children (safe in children above 7

years of age with normal intellect) , geriatric age group, and patients with opioid tolerance

Overdosage can result in decreased respiratory effort, rate and depth, nausea/vomiting, pruritis and urinary retention.

Monitoring of adverse effects:

There must be a standardized scale for assessing the level of pain (Visual Analogue Score, Numerical Rating Score, etc.) in all patients receiving PCA. The basic monitoring should involve the assessment for signs of excessive sedation. Patients' level of alertness, vital signs, respiratory rate and the quality of respiration should be examined every 4 hours (115).

Monitoring should be more vigilant in the first 24 hours , and particularly during night time as patients are more prone for hypoventilation followed by hypoxia due to respiratory depression. The heathcare personnel should be familiar with the use of naloxone for opioid toxicity.

The PCA settings have to be cross checked and verified after every shift and titrated according to the patient needs. Refilling should be done carefully to avoid filling of wrong concentration mixtures.

QoR 15 SCORE

An important measure of post surgical health status among patients is the 'quality of recovery' score, a fairly new 'Patient Reported Outcome Measure' (PROM) (116). The score is a reliable, valid system that assesses the global recovery status of patients by analysing five dimensions of health, i.e., emotional state, physical comfort, psychological support, physical independence and pain by using a set of 15 questions. Surgery and anaesthesia mostly affect the patients physical comfort, physical independence and pain. The maximum score possible is 150 and the minimum is zero. A poor recovery score translates to increased hospital duration (117) and expenses.

QoR – 15 is essentially derived from a 40 item questionnaire - QoR – 40, which has excellent validity, reproducibility and clinical acceptability. However, QoR – 40 is relatively unfavourable since a long duration of about 10 minutes is required to complete the questionnaire whereas time taken to complete the QoR-15 is 2.4 ± 0.8min (mean ± SD) (118). QoR – 15 was also found to be valid in a wide variety of surgeries and is the first recovery measurement tool to undergo a systematic review (116). Peter Stark concluded that it was not necessary to have a minimum fixed interval between two scores and 30 – 60 minutes were enough to demonstrate and compare any significant changes in the postoperative period (118).

JUSTIFICATION FOR THE TRIAL

A Cochrane review in 2015 (23) of 45 randomised control studies on the effects of intravenous lidocaine bolus and infusion in comparison to several other pain relief modalities showed a better analgesic profile with lesser requirements of opioids both immediately and upto 24 hours after the surgery in most of the studies. For the most part, the studies also showed a decrease in post-operative nausea and vomiting, a faster onset of bowel movements, reduced risk of paralytic ileus , a shorter hospital stay , all of which are predictors of the quality of recovery of patients. Also, our aim was to reduce the general opioid consumption, particularly, morphine, which has been repeatedly shown to enhance tumor recurrence in colon cancers.

Thus, there is a possibility of potential improvement in the overall recovery of these patients.

There is still a scarcity of data regarding optimal dose, timing, duration and bolus requirement of lidocaine. In addition to pain scores, we sought to assess the quality of recovery as one of the outcomes using QoR 15 score.

The majority of the studies have compared intravenous lidocaine to placebo. Only a few studies have compared intravenous lidocaine with thoracic epidural. However, their primary objective was to compare the return of gastroinstestinal functions and length of hospital stay. We planned, in our study, to compare between intravenous lidocaine and Throacic Epidural, their efficacy in post operative pain management. A difference of 10 points in QoR15 score was considered significant, to say intravenous

lidocaine technique was better than thoracic epidural. Our other secondary outcomes were postoperative opioid consumption, duration of hospital stay, any side effects associated in either of the two study groups.

ECONOMIC FACTORS AND AVAILABILITY

Lidocaine is an essential drug on World Health Organisation (WHO)'s essential drug list. It is available in the generic form and in majority of the developing countries at a reasonable price. (50cc of 2% lidocaine at Rs.40).

This widespread availability in rural areas of India, makes it a feasible and attractive option for delivering safer anaesthesia for laparoscopic surgeries. Preliminary studies in lidocaine infusion perioperatively, has shown potential, but there is deficiency in data on the correct use of this mode of analgesia from developing countries like India and none from this subset of patients.

METHOD

DESIGN

The study is a prospective, parallel group, randomised control trial.

The study is designed in accordance to the CONSORT 2010 and SPIRIT 2013 guidelines.

The allocation ratio for the study is 1:1.

There were two arms in the study.

- **Intervention arm A**: Lidocaine group.
- **Intervention arm B**: Thoracic Epidural Analgesia (TEA) group.

The patients were randomly allocated to the two groups.

Both the arms were administered the standard general anaesthesia drugs.

- **Intervention arm A**: In addition, lidocaine bolus and infusion was administered perioperatively.
- **Intervention arm B**: Thoracic Epidural catheter was inserted before induction of anaesthesia and continued for 48 hours.

There were no major changes to the study design after the commencement of the study.

INCLUSION CRITERIA

- All patients undergoing laparoscopic Anterior Resection/ Low Anterior Resections/ Ultra Low Anterior Resection/ Sigmoid Colectomy for either cancerous / non cancerous lesions.
- Age > 18 yrs
- ASA 1 & 2

EXCLUSION CRITERIA

- ASA 3 & 4
- Electrolyte disturbances
- Allergy to local anaesthetic
- Seizure disorder
- Anti-arrhythmic drug intake within 1 week before surgery
- Psychiatric disorders
- Steroid treatment
- Chronic opioid treatments
- Conversion to laparotomy

CRITERIA FOR EXCLUDING A PATIENT FROM THE TRIAL AFTER BEGINNING THE STUDY

- Participant request for exclusion from trial
- Hypersensitivity reactions
- Conversion of laparoscopic surgery to open surgery
- Conversion of the planned surgical procedure to a different procedure intra-operatively or abandonment of the planned procedure due to inoperability.

PARTICIPANT TIMELINE

Enrolment of patients, recruitment and intervention was done over 14 months. This was followed by data analysis and interpretation of results over the next 2 months.

CONSORT 2010 FLOW DIAGRAM

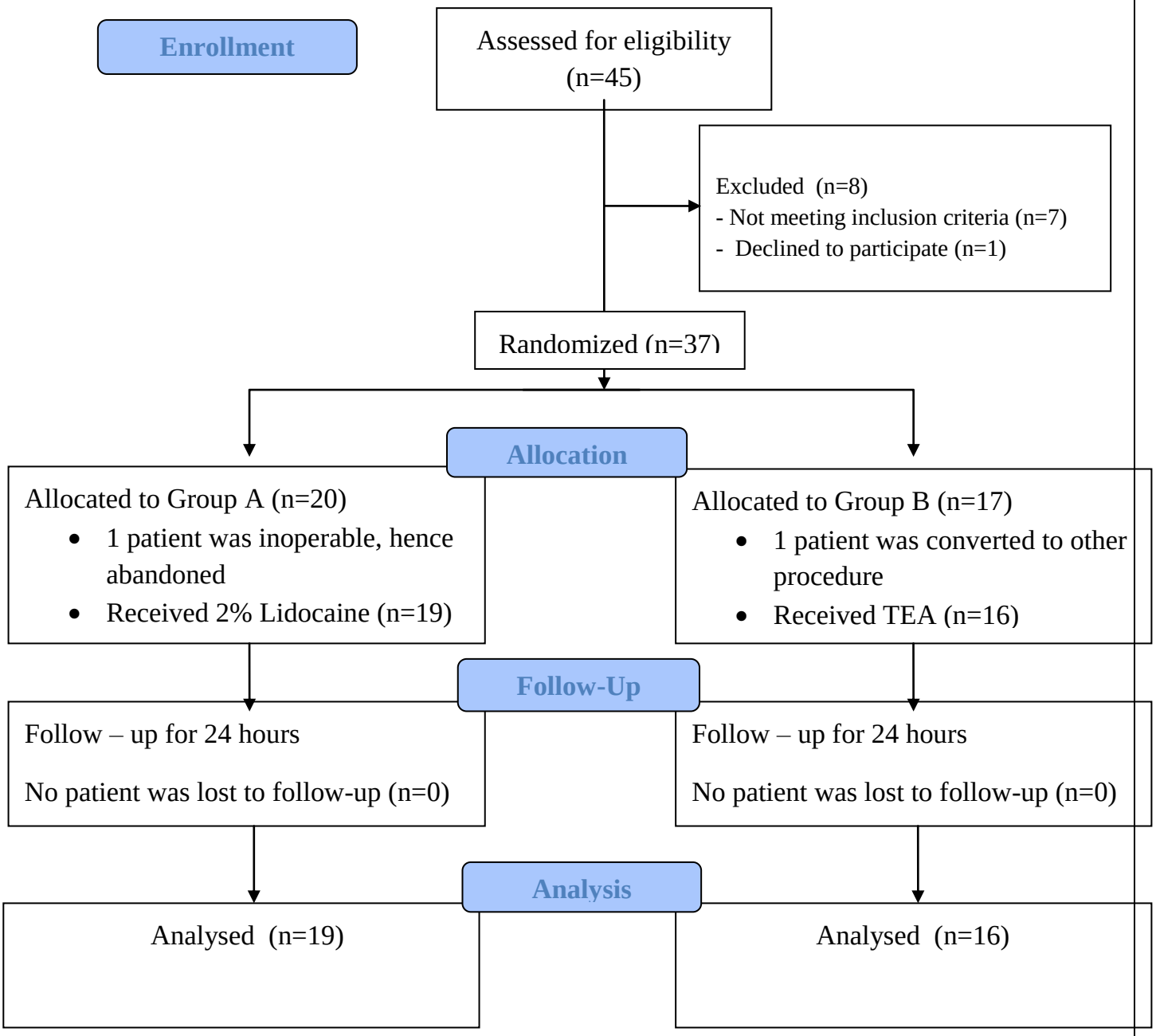


Figure 7 : Consort Diagram

SETTING & LOCATION

The study was conducted in Christian Medical College Vellore. Our Institute is a tertiary referral centre in South India. The subject sample was drawn from the pool of patients undergoing elective Laparoscopic Anterior Resection/ Low Anterior Resection/Ultra Low Anterior Resection/ Sigmoid Colectomy for cancerous and non cancerous lesions of the colon.

In our institute, 30 - 40 elective laparoscopic colorectal surgeries are performed every year.

The patients once posted for surgery, if fulfil the inclusion and exclusion criteria, are recruited for the study. Since the hospital is a referral centre, the patients are from various ethnic backgrounds.

SAMPLE SIZE

With reference to R. Tikuisˇis etal ; Tech Coloproctology (2014) 18:373–380 (21), the maximum Standard deviation assumed to be 1.6 in both the groups with a clinically expected difference in NRS scores to be 1.5 units with alpha error fixed at 5% with power at 80% for a two sided test we need to study atleast 18 subjects who undergo surgery.

Two Means - Hypothesis testing for two means	
Standard Deviation in group A (Lidociane)	1.6
Standard deviation in group II (TEA)	1.6
Mean difference	1.5
Effect size	0.9375
Alpha error (%)	5
Power (1- beta) %	80
1 or 2 sided	2
Required sample size per group	18

The sample size was calculated using the following formula (Non-inferiority - Two Groups - Parallel - Two proportions – Equal Allocation).

Formula

$$n = \frac{2{s_p}^2\left[Z_{1-\alpha/2} + Z_{1-\beta}\right]^2}{\mu_d^2}$$

$$s_p^2 = \frac{s_1^2 + s_2^2}{2}$$

Where,

S_1^2 : Standard deviation in the first group

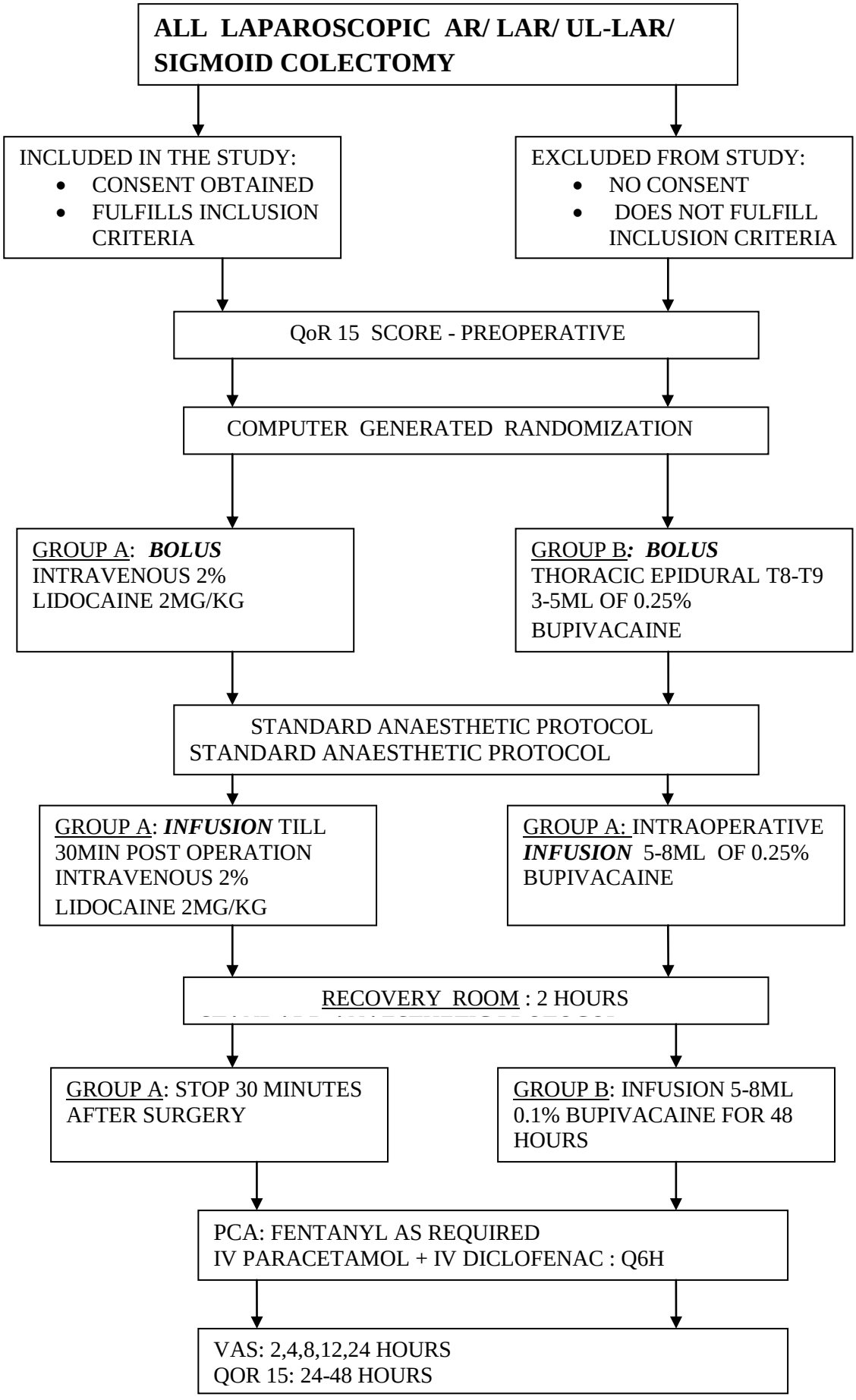
S_2^2 : Standard deviation in the second group

μ_d^2 : Mean difference between the samples

α : Significance level

1- β : Power

Figure 8: DETAILED METHODOLOGY



Patients who were admitted for Laparoscopic Anterior Resection (AR)/ Low Anterior Resection (LAR)/ Ultra - Low Anterior Resection (UL - LAR)/ Sigmoid Colectomy, who met the inclusion criteria (ASA I and II, Age >18 years) were approached and explained about the details of the study. A written, informed consent was taken from those who were willing to participate in this study. The patients who consented were recruited.

A computer generated randomization allocated the patients into two groups. Group A received intravenous lidocaine, Group B had, in place, a Thoracic Epidural catheter either in eighth – ninth or ninth – tenth thoracic intervertebral space before induction of general anaesthesia. A baseline QoR 15 score was performed by the primary investigator preoperatively in the ward for all recruited patients.

Just before induction of anaesthesia, patients assigned to Group A received lidocaine intravenous bolus injection of 2 mg/kg followed by a continuous infusion of 2mg/kg/hr which was continued till 30 minutes into the recovery room. For safety reasons, the lidocaine infusion was connected to the distal part of the intravenous line to avoid accidental bolus administration.

Patients assigned to the Group B had Thoracic Epidural Catheter inserted before induction of general anaesthesia. A bolus of 3-5 ml of 0.25% Bupivacaine was given, followed by an infusion at 5-8ml/hr to provide bilateral segmental sensory block between T7 and L3 dermatomes.

All patients were induced with Inj. Fentanyl upto 2 mcg/kg and Inj. Propofol 2 mg/kg and orotracheal intubation was achieved with Inj. Vecuronium (0.1 mg/kg at induction and later as required). Inj. Paracetamol 15 – 20 mg/kg was given after induction for

analgesia. Supplemental doses of 0.5 - 1 mcg/kg of fentanyl was given according to the pain response . i.e. when intraoperative blood pressure and heart rate were 20% greater than those of baseline.

Intraoperative hemodynamics was maintained with fluids upto 5-8 ml/kg/h. Local infiltration with 0.25% bupivacaine at port site was also given for analgesia at the end of surgery. Patients were extubated after meeting the extubation criteria and were shifted to recovery room.

Lidocaine infusion was continued for half an hour and the patient was monitored till discharge from the recovery room. Epidural infusion with 0.1% bupivacaine + 2mcg/ml fentanyl at 5 – 8 ml/hr was continued till 48 hours postoperative. Systolic, diastolic, mean blood pressure , heart rate and saturation was recorded at baseline, post induction and post extubation in the recovery room. Thereafter, haemodynamic parameters were recorded every 30 minutes till patient was discharged to the ward. Intraoperative total analgesic (fentanyl, morphine, paracetamol, tramadol, NSAIDS) used was recorded.

All patients received intravenous bolus dose of fentanyl 20 mcg at a lockout period of 15 minutes through patient controlled drug delivery system (CADD Pump) for 24 hours postoperatively along with Paracetamol 20mg/kg 6^{th} hourly.

In the ward, all patients were seen by the anaesthesia pain team and the primary investigator. The following parameters were recorded -

- Numerical Rating Score (NRS) at 2,4,8,12,24 hours
- QoR 15 score at any time between 24 - 48 hrs postoperative

- Total analgesic consumption (Total Fentanyl pulses from CADD pump)
- Duration of hospital stay

At the end of the study all the data were analysed and reported.

RECRUITMENT

All patients who consented for the study and fulfilled the inclusion criteria were recruited by the principal investigator for the study. Institutional Review Board clearance and Ethics Committee approval were obtained before the start of the study.

ASSIGNMENT OF INTERVENTION

Method of Generating Randomisation:

The study patients were randomly allocated to Group A and Group B using computer generated randomisation.

Method of Allocation Concealment:

Sequentially numbered, sealed, opaque envelopes were made by a person not involved in the study, and were opened by the anaesthetist not involved directly in the study, in the operation theatre. The sealed envelope would give instructions to either load 2 % lidocaine into a 50cc disposable syringe or prepare for TEA based on the randomisation.

DATA MANAGEMENT

Data Collection Methods:

The anaesthesia provider assigned for the surgery recorded all the readings. The primary investigator describes the methodology and documentation required during the surgery to the primary and secondary anaesthesia provider. Blood pressure readings should be documented at specific time points, but this was not very cumbersome. Time points during the surgery, such as time to extubate had to be documented. This was reinforced by requesting the anaesthesia provider to add a timer to the anaesthesia monitors in addition to noting the time from the clock.

The health care providers in the recovery room were also trained to document the haemodynamic recordings, conduct pain assessment using the Numerical Rating Scale and educate the patient, when fully awake, regarding the use of Patient Controlled Analgesia (PCA). Real time logging is done by the various monitors, which does not hamper the care being given to the patient.

The data collection sheet was provided to the anaesthesia team which had to be accurately filled up and rechecked by another member of the same team.

The data collection forms can be found in the annexure.

Data Quality:

The data collection sheets are checked within 6 hours of surgery by the primary investigator and the pain team in post operative ward for the following -

- Repeated entries
- Incorrect entries
- Missing entries

In case of the above, the anaesthesia providers check the PCA monitor for stored data. If the data is not retrievable then it is entered as missing data.

Data Security and Storage:

We currently do not own a data storage facility. The hard copies of all the data collection sheets and informed consent forms are stored by the primary investigator.

Patient confidentiality is preserved as the raw data with coded patient details are provided to the statistician. The key to the code remains with the primary investigator. Subject details are not divulged without the expressed written permission of the study subject.

STATISTICAL METHODS

Data were entered in Epidata software and analysis was done using SPSS software. Descriptive statistics was reported using Mean +/- SD for continuous variables. Categorical variables was reported using Frequency and percentage. The data which is normally distributed is reported as Mean +/- SD. Bar graphs and line diagrams are used for graphical representation of data. Based on the normality of the data, either parametric t test or non parametric Mann-Whitney test was applied. Comparison of means between the two arms for continuous variables was done using Two independent sample t test. Association between the arms with respect to the categorical variable was reported using Chi square/Fisher's exact test. The primary outcome was to assess postoperative pain. A two sample T-test was applied to calculate significance between the two arms. The two sample t was also used to analyse demographics (age, weight, height, BMI), baseline vitals, rescue analgesic dose given and change in the QoR – 15 score.

All tests were two-sided at $\alpha=0.05$ level of significance. All analyses was done using Statistical Package for Social Services (SPSS) software Version 21.0 (Armonk, NY: IBM Corp).

ETHICS AND DISSEMINATION

INSTITUTIONAL REVIEW BOARD APPROVAL:

The Office of Research, Institutional Review Board (IRB) approval was obtained on March 20, 2017. The IRB Min. reference number is 10542. The Approval can be found in the annexures.

CONSENT & ASSENT

The primary investigator obtained informed consent from the potential trial participants or authorised surrogates.

The consent form was provided to the trial participant or authorised surrogate in a language they could understand. The details of the study were explained to them and doubts were clarified. Emphasis was laid on the fact that the treatment of the patient would not differ in any way even if they did not provide consent/assent to the study.

Access to Data: The primary investigator will keep the data confidential. Even in the event of dissemination of the raw data, the patient details will be coded and the key will be retained with the primary investigator.

Ancillary and Post Trial Care: There are no provisions for ancillary and post-trial care or compensation to those who suffer harm from trial participation. This is because both lidocaine infusion is well studied , used widely as an antiarrhythmic without major complications at doses being used for the trial.

DISSEMINATION POLICY:

Trial Participants: It is not intended to communicate the trial results to the participants.

Publication: If the study is published, there is no intention to use professional writers. The primary investigator will be the first author and the guide and co guide will be the second and third author respectively.

Public access: It is not intended to provide public access to the full protocol.

RESULTS

The data collected has been analysed under the following headings:

1) Pre – operative parameters
2) Intraoperative parameters
3) Post – operative parameters

1) PRE –OPERATIVE PARAMETERS :

The total number of patients that were recruited for the study was 37 out of which 20 patients were randomized to Group A and 17 patients to Group B. Among the patients who were included in the study, one patient in Group A was excluded from analysis, since the surgeons, after a check laparoscopy under anaesthesia, decided that the tumor was inoperable. One patient in Group B was also excluded as the surgeons decided to proceed to Laparoscopic Abdominoperineal Resection, which is not the surgical procedure of interest in this study.

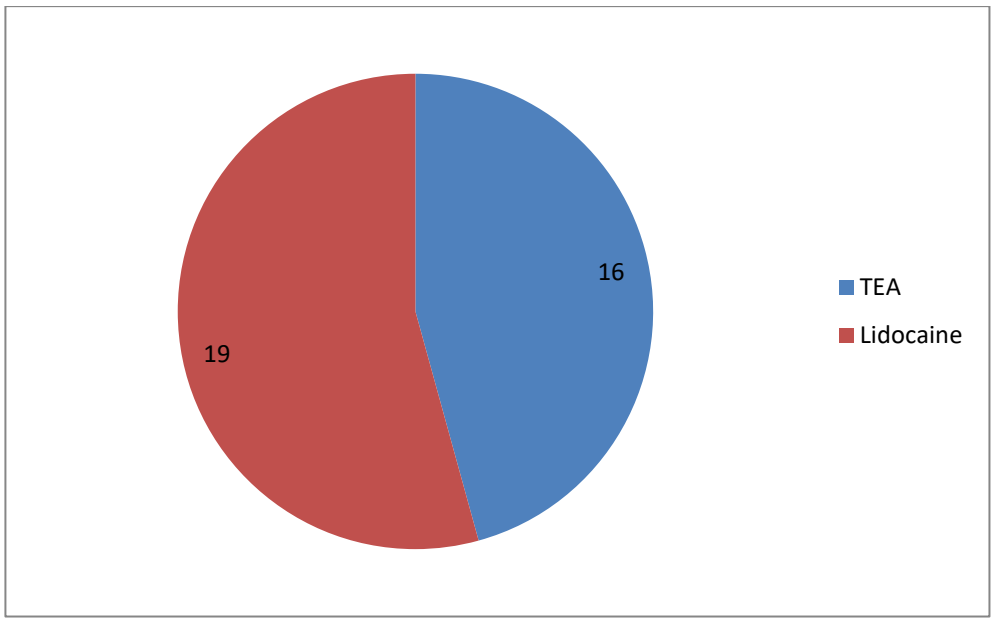


Figure 9: Total No. Of patients analysed n = 35

DESCRIPTIVE STATISTICS:

Table 1 : Demographic details of the study patients

Parameters	Group A IV Lidocaine (N = 19)	Group B TEA (N = 16)	p value
Age (years)	47.7 ± 15.8	51.1 ± 12.4	0.492
Weight (Kg)	67.5 ± 12.0	60.7 ± 5.4	0.046
Height (Cm)	162.5 ± 10.9	163.2 ± 7.8	0.814
Gender (M:F)	13 (68.4%): 6 (31.6%)	11 (68.8%): 5 (31.2%)	0.983
ASA 1 ASA 2	11 (57.9 %) 8 (42.1 %)	7 (43.8 %) 9 (56.2 %)	0.404 0.404
BMI	25.5 ± 4.0	23.0 ± 2.7	0.049

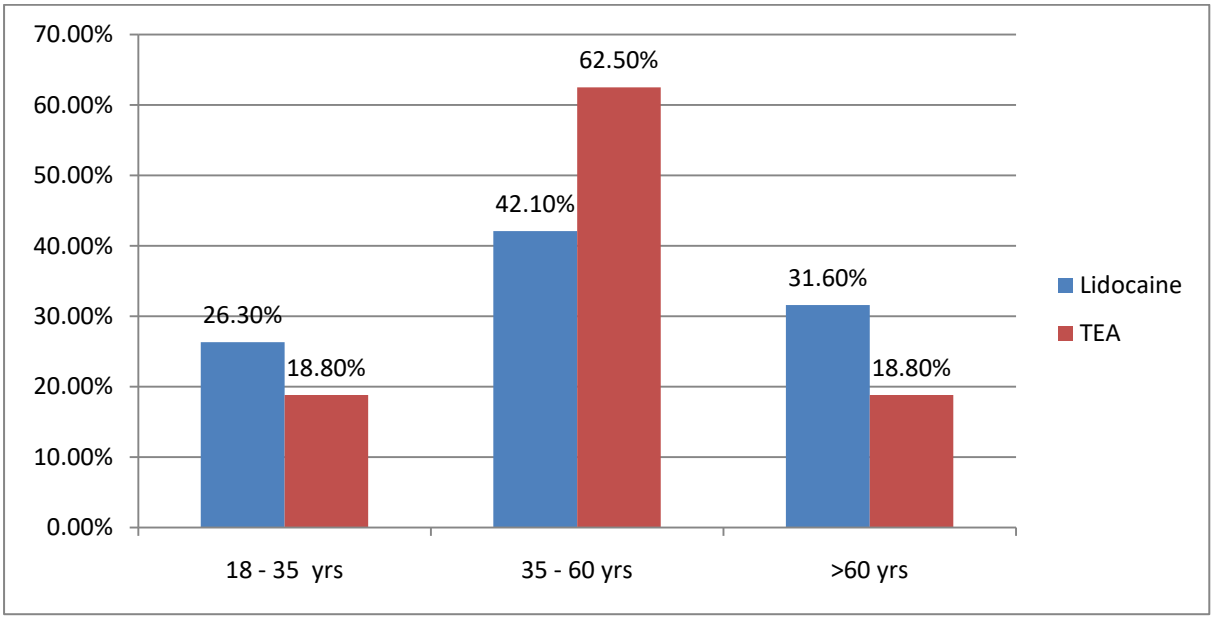


Figure 10 : Age distribution among the patients. Most of the patients were aged between 35 – 60 years.

5 (26.3%) patients in group A and 3 (18.8%) in group B were aged between 18 – 35 years. 8 (42.1%) patients in group A and 10 (62.5%) patients in group B were aged between 35 – 60 years. 6 (31.6%) patients in group A and 3 (18.8%) patients in group B were > 60 years. Comparison was done using Chi – square test and p value is 0.550. Thus both groups were comparable and there was no significant difference in age distribution.

24 out of 35 patients were males (68.6%), whereas 11 (31.4%) were females. In Group A (Lidocaine), 13 patients were males and 6 were females. In Group B (TEA), 11 patients were males and 5 were females.

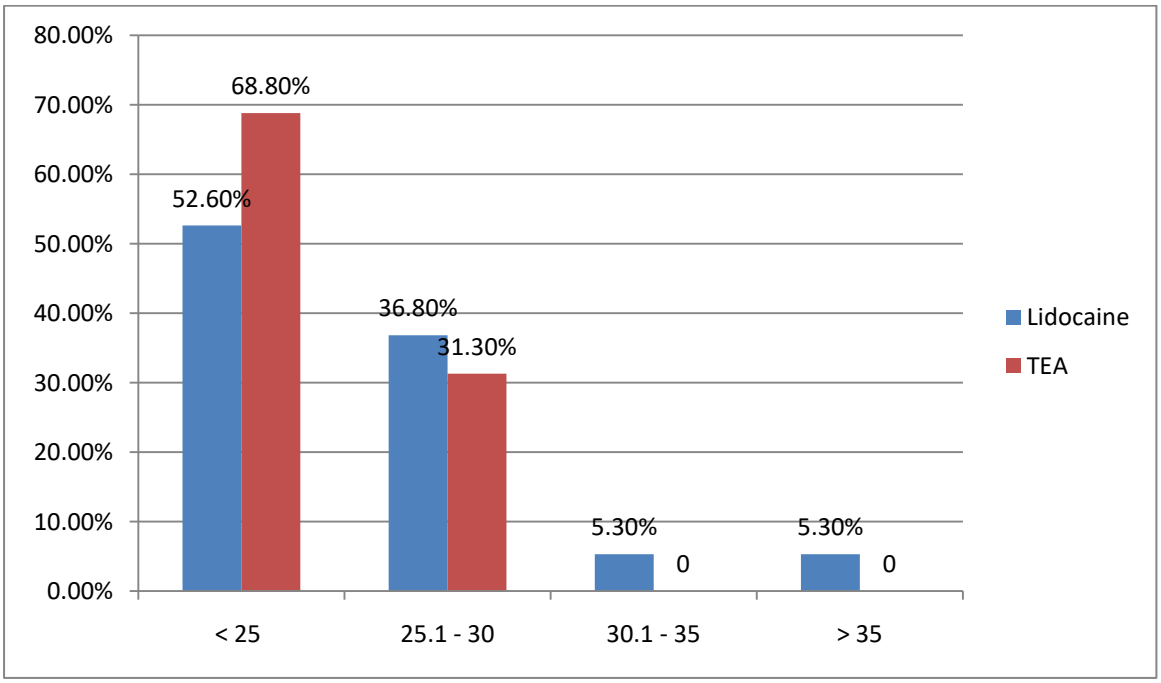


Figure 11 : Distribution of BMI in both groups

52.6 % of patients in group A and 68.8% in group B were in the normal range of BMI (< 25 kg/m^2) ; 36.8% in group A and 31.3% in group B were overweight (BMI – 25.1 – 30 kg/m^2) ; two (5.3%) patients in group A were obese (BMI > 30 kg/m^2) and none were obese in group B.

Patients above the age of 18 years were included in the study. The average age of the participants in both groups is comparable. As this is a parametric variable, independent sample t – test was used to analyse the data. The p value is 0.492, suggestive of no significant difference in the age of the patients included in both groups of the study. The mean age of the affected population was 49 years. According to the Surveillance, Epidemiology, and End Results (SEER) Program (119), the median age at diagnosis is 67 years for colorectal cancer.

The average weight and BMI of the population in group B was slightly lower as compared to group A.

ASA Risk Distribution

Only grade 1 and 2 were included in the study, out of the six categories of physical status classification by the American Society of Anaesthesiologists (ASA) .

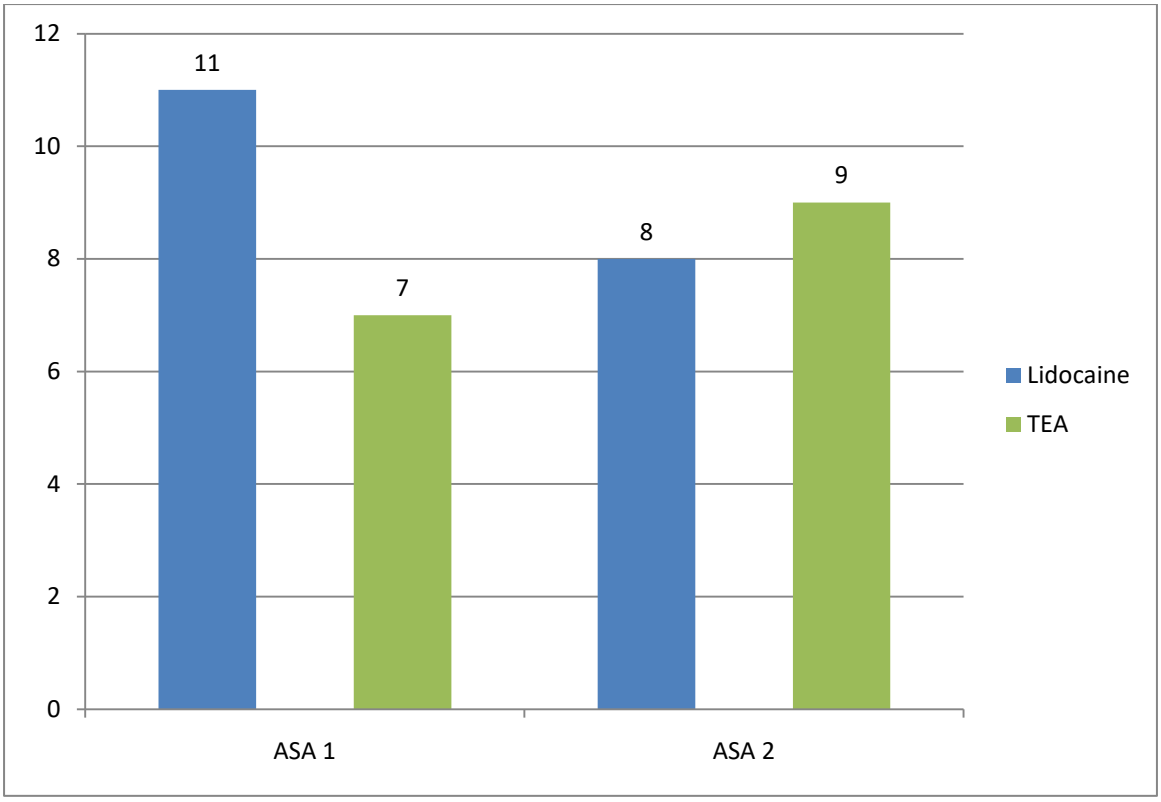


Figure 12 : Y-axis - Number of study subjects in each ASA group

ASA grade 1 = A normal healthy patient.

ASA grade 2 = A patient with mild systemic disease (Mild diseases only without substantive functional limitations)

The Lidocaine Group - A had 8 ASA-2 patients, 11 ASA-1 patients. The TEA Group - B had 7 ASA-1 patients and 9 ASA-2 patients. 57.9 % in Group A and 43.8 % in Group B belonged to ASA grade 1. Patients taking any anti – arrhythmic drugs were excluded from the study to prevent any unwanted side effects of Lidocaine like bradycardia and hypotension. Since patients with uncontrolled diabetes mellitus

belong to ASA III category, such patients were excluded from the study. The ASA grade 2 patients included in the study were mostly patients with Diabetes Mellitus, Hypertension or Hypothyroidism. 42.1 % of patients in Group A and 56.2 % of patients in Group B belonged to ASA grade 2. There was no significant difference between the two arms pertaining to the distribution of ASA 1 and 2 categories.

Table 2 : Comorbidities among the study patients (n%)

Parameters	**Group A** **IV Lidocaine** **(N = 19)**	**Group B** **TEA** **(N = 16)**	**P value**
Hypertension	6 (31.6 %)	5 (31.2 %)	0.983
Diabetes	2 (10.5%)	2 (12.5%)	1.000
Allergies	0 (0.0 %)	2(12.5 %)	0.202
Hypothyroid	1 (5.3%)	2 (12.5%)	0.582
Previous surgery	6 (31.6%)	2 (12.5%)	0.451

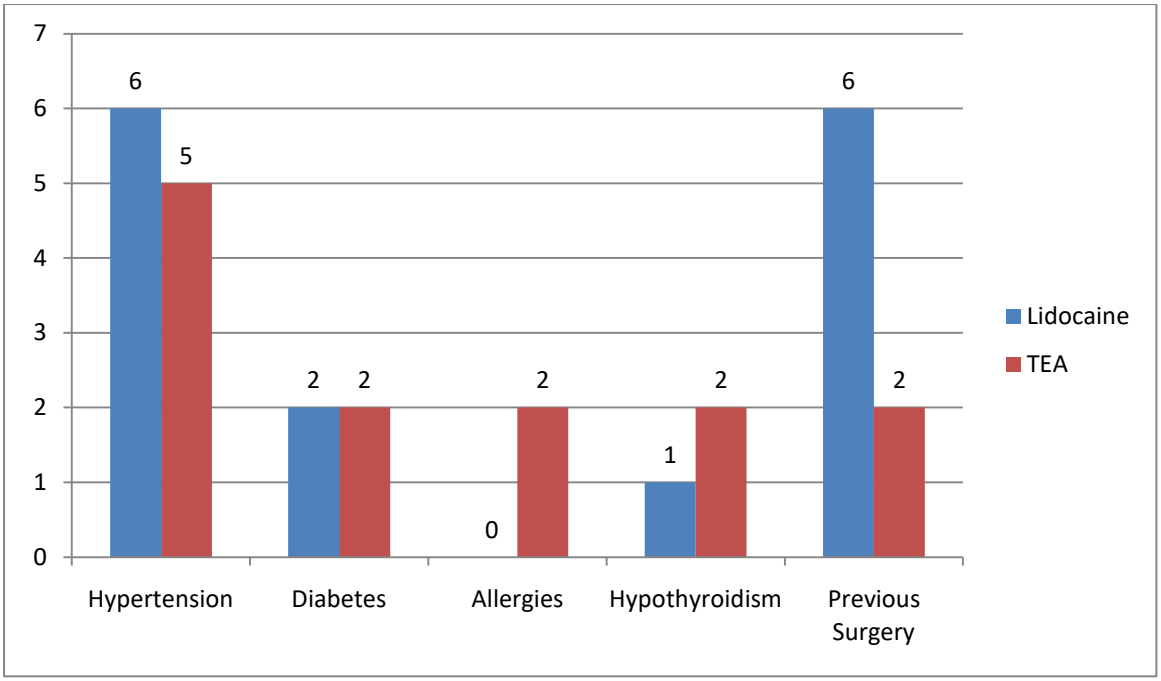


Figure 13 : Distribution of comorbid illnesses. Most of the patients recruited were hypertensives.

As is evident from the above table, hypertension was the most common comorbid illness associated in the study population. All the patients were well optimized preoperatively. There is no significant difference in the distribution among both groups. Two patients in group B were allergic to antibiotics and included in the study. None of the patients gave a history of chronic pain, psychiatric illness, postoperative nausea and vomiting or motion sickness.

There have been studies in the past which have concluded that certain comorbidities affect the pain threshold, pain impulse conduction and the total analgesic consumption. For example, patients with ***uncontrolled Diabetes*** habitually have associated neuropathy. Likewise, patients with Chronic Kidney Disease may have to

be administered lower doses of opioids. For this reason, patients with such comorbidities were excluded from the study.

The patients with a history of previous surgery and allergies were also distributed evenly among the three groups (no $p < 0.05$)

Table 3: Baseline vital parameters between the two groups (Mean ± SD)

Parameters	Group A IV Lidocaine (N=19)	Group B TEA (N=16)	p value
Systolic BP (mmHg)	130.3 ± 19.7	132.4 ± 13.6	0.719
Diastolic BP (mmHg)	79.4 ± 7.9	80.9 ± 7.4	0.552
MAP (mmHg)	96.2 ± 10.2	98.2 ± 8.6	0.532
Heart rate (/min)	84.2 ± 10.9	85.9 ± 11.1	0.660
Respiratory rate (/min)	15.6 ± 2.7	15.9 ± 2.7	0.741

The baseline preoperative vital parameters were collected. This was analysed using independent sample t test. The systolic blood pressure mean among the two groups was around 130 mmHg, mean diastolic blood pressure ranged between 79 - 81 mmHg and the mean MAP was between 96 – 98 mmhg ; p value was 0.719, 0.552 and 0.532 respectively.

The mean heart rate between the two groups was from 84 - 86 beats/min, p value 0.660 and the mean respiratory rate 15-16, p value 0.741.

The baseline vital parameters did not show any significant statistical difference between the two study groups.

Type of Surgery underwent in each group:

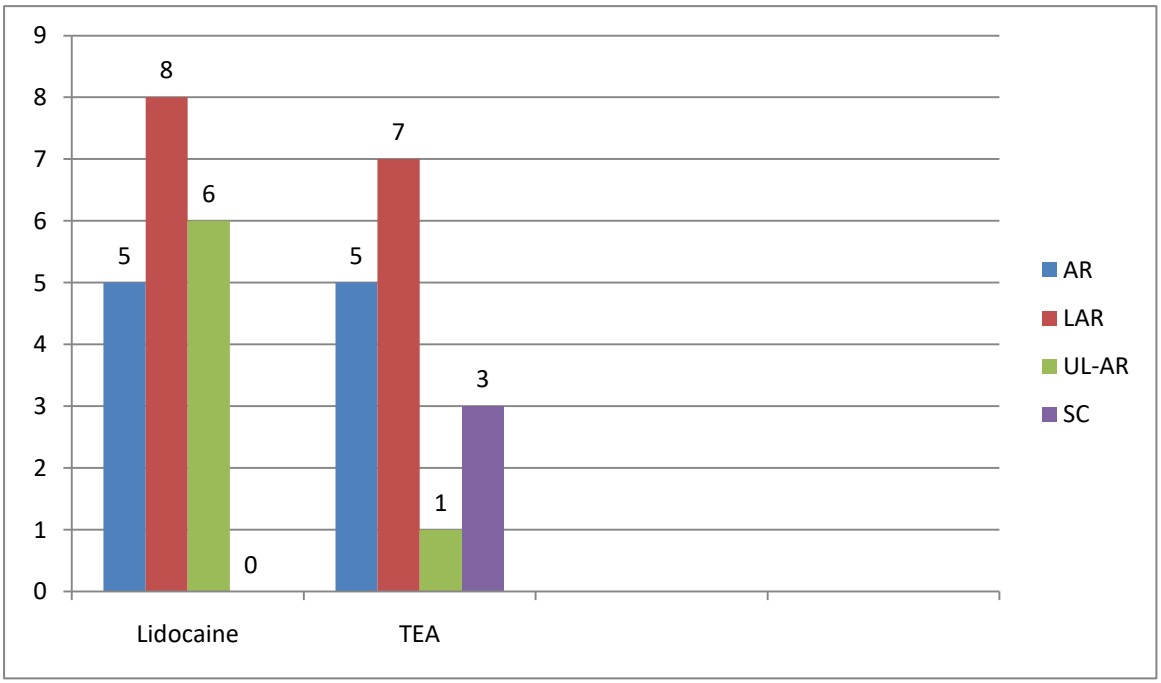


Figure 14 : Type of surgery; Y – Axis – Number of patients undergoing AR – Anterior Resection, LAR – Low Anterior Resection, UL – LAR – Ultra Low Anterior Resection, SC – Sigmoid Colectomy

5 (26.3 %) patients in Group A and 5 (31.2 %) patients in Group B underwent laparoscopic Anterior Resection. While there were 8 (42.1 %) patients in Group A and 7 (43.8 %) patients in Group B who underwent the Low Anterior Resection, only 1 (6.2 %) patient underwent Ultra – Low Anterior Resection in Group B as compared to

6 (31.6 %) patients in Group A. 3 (18.8 %) patients in Group B underwent Sigmoid Colectomy while there were none in Group A.

Thus most of the patients studied in both arms underwent Low Anterior Resection.

2) INTRAOPERATIVE PARAMETERS:

Table 4 : Comparison of the mean duration of surgery

Parameters	Group A IV Lidocaine (N = 19)	Group B TEA (N = 16)	P value
Duration of surgery (min)	281.0 ± 73.9	234.4 ± 74.6	0.073
Duration of anaesthesia (min)	335.5 ± 75.3	299.0 ± 79.6	0.174
Duration of Lidocaine infusion (min)	368.9 ± 75.9	-	-
Time to extubation (min)	14.5 ± 5.8	14.0 ± 3.9	0.788

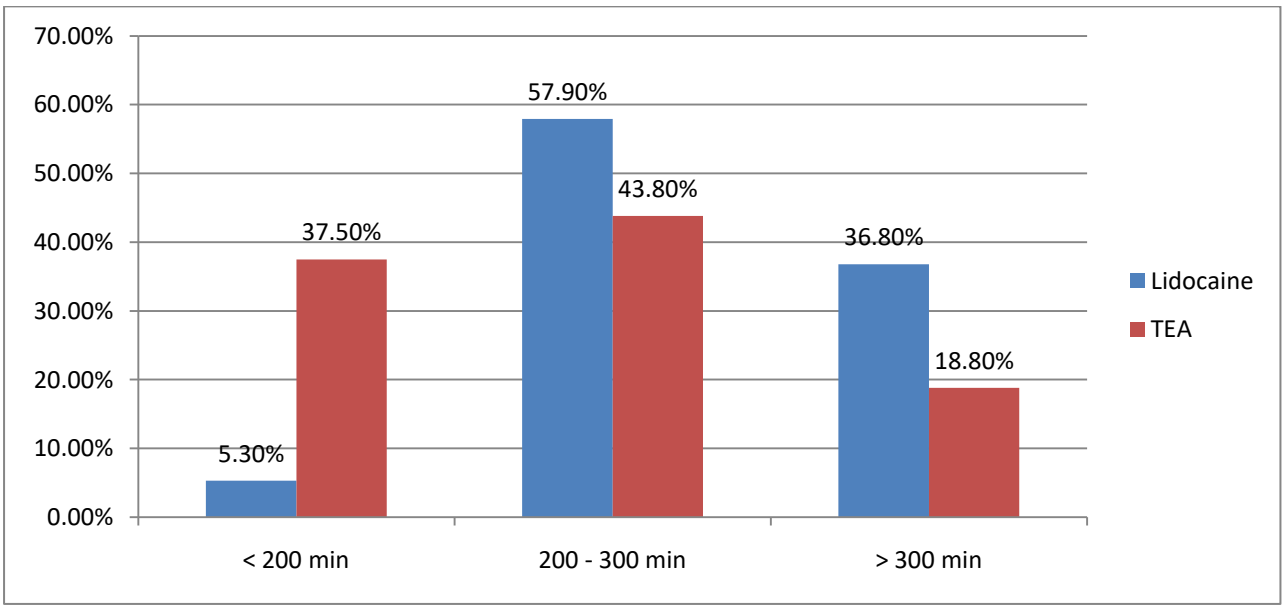


Figure 15: Duration of surgery; 1 (5.3%) patient in group A and 6 (37.5%) patients in group B had the surgery in < 200 minutes ; 11 (57.9%) in group A and 7 (43.8%)

patients in group B required a surgical duration of 200 – 300 minutes. 7(36.8%) in group A and 3(18.8%) patients in group B had a surgical duration of > 300 minutes.

The total duration of surgery (this was the time measured from skin incision to skin closure) was approximately 281 minutes for Group A and around 234 minutes for Group B; p value is 0.20 and hence not of statistical significance.

The duration of anaesthesia (this was the time from the start of induction to the time of extubation) was 335 minutes for Group A and 299 minutes for Group B. The duration of surgery was analysed to know the average surgical time in both groups. There was no significant difference in the duration of surgery in both the groups.

The time taken to extubate was measured from the minute of cutting off the inhalational anaesthetic agent till the patient was fully awake. There was no difference in the time taken to extubate the patients in both groups. Patients took an average of 14.2 minutes to wake up in both the groups. Lidocaine was infused for a maximum duration of 510 minutes without any adverse effects.

Table 5 : Intraoperative use of Analgesics

Parameters	Group A IV Lidocaine (N = 19)	Group B TEA (N = 16)	P value
Fentanyl (mcg)	207.9 ± 55.0	183.8 ± 55.0	0.205
Morphine (mg)	4.4 ± 2.7	4.8 ± 1.2	0.766
NSAIDS (mg)	68.7 ± 12.5	50.0 ± 0.0	0.272
Tramadol (mg)	75 ± 28.9	100	0.495

The table above shows all the intraoperative parameters that were analysed, presented as mean and standard deviation. The analgesics, in particular, the total opioid consumption during the surgery, was documented and compared. The drugs used for analgesia were morphine, fentanyl , tramadol, NSAIDS (diclofenac) and paracetamol. Paracetamol (20 mg/kg) was given to all patients. Fentanyl 2 mcg/kg was used during induction of anaesthesia. Further stress response was treated with 0.5 mcg/kg fentanyl, upto a maximum dose of 5 mcg/kg. The overall requirement of fentanyl was in the range of 180 – 210 mcg in both groups; p value was 0.205. Morphine was given via intravenous route. The mean dose administered was in the range of 4.4 – 4.8 mg and p value was 0.766. Tramadol (75 – 100 mg) was administered to 4 patients in Group A and 1 patient in Group B. Longer surgeries may require higher quantities of drugs and may imply a greater surgical difficulty and hence greater pain. However, there was no significant difference in the total analgesics administered in both the groups.

Table 6 : Intraoperative Fluids and Blood loss

Parameters	Group A IV Lidocaine (N = 19)	Group B TEA (N = 16)	P value
Blood loss (ml)	141.0 ± 61.0	137.5 ± 53.2	0.857
Total Fluids (ml)	1500 ± 596.3	1525 ± 628.6	0.905
Crystalloid (litre) Colloid (litre)	1.4 ± 0.5 0.4 ± 0.2	1.6 ± 0.5 0.6 ± 0.3	0.502 0.242

The total blood loss in both groups was around 138 – 140 ml, this was not of statistical significance as the p value was 0.857.

The total amount of intravenous fluids used was 1500 – 1525 ml. Lidocaine group was administered an average of 1.4 L crystalloids and 0.4 L colloid whereas TEA group received 1.6 L crystalloids and 0.6 L colloid. Even though there was slightly higher fluid consumption in Group B (TEA), it is not statistically significant (p value 0.905). None of the patients required blood transfusion.

3) POST - OPERATIVE PARAMETERS:

Table 7: Post operative pain scores in the Post Anaesthesia Recovery Room (PACU)

Time	5 minutes	30 minutes	1 hr	1.5 hrs	2 hrs
Group A (mean±SD)	1.8 ± 2.4	2.4 ± 2.5	3.2 ± 2.8	3.4 ± 2.6	3.5 ± 2.5
Group B (mean±SD)	1.1 ± 2.1	1.5 ± 2.5	2.1 ± 2.7	2.2 ± 1.8	2.2 ± 1.9
p - value	0.356	0.281	0.230	0.136	0.121

The postoperative pain was measured using the numerical rating scale (NRS), a scale from 0 to 10 which entails no pain to the worst pain possible. A score less than 4 was acceptable and anything more than four had to be treated (A score of 1 – 3 is considered mild pain, 4 – 6 is moderate and 7 – 10 is severe pain)

All the patients in the recovery room had a pain score of < 4 and there was no statistical difference between both the groups.

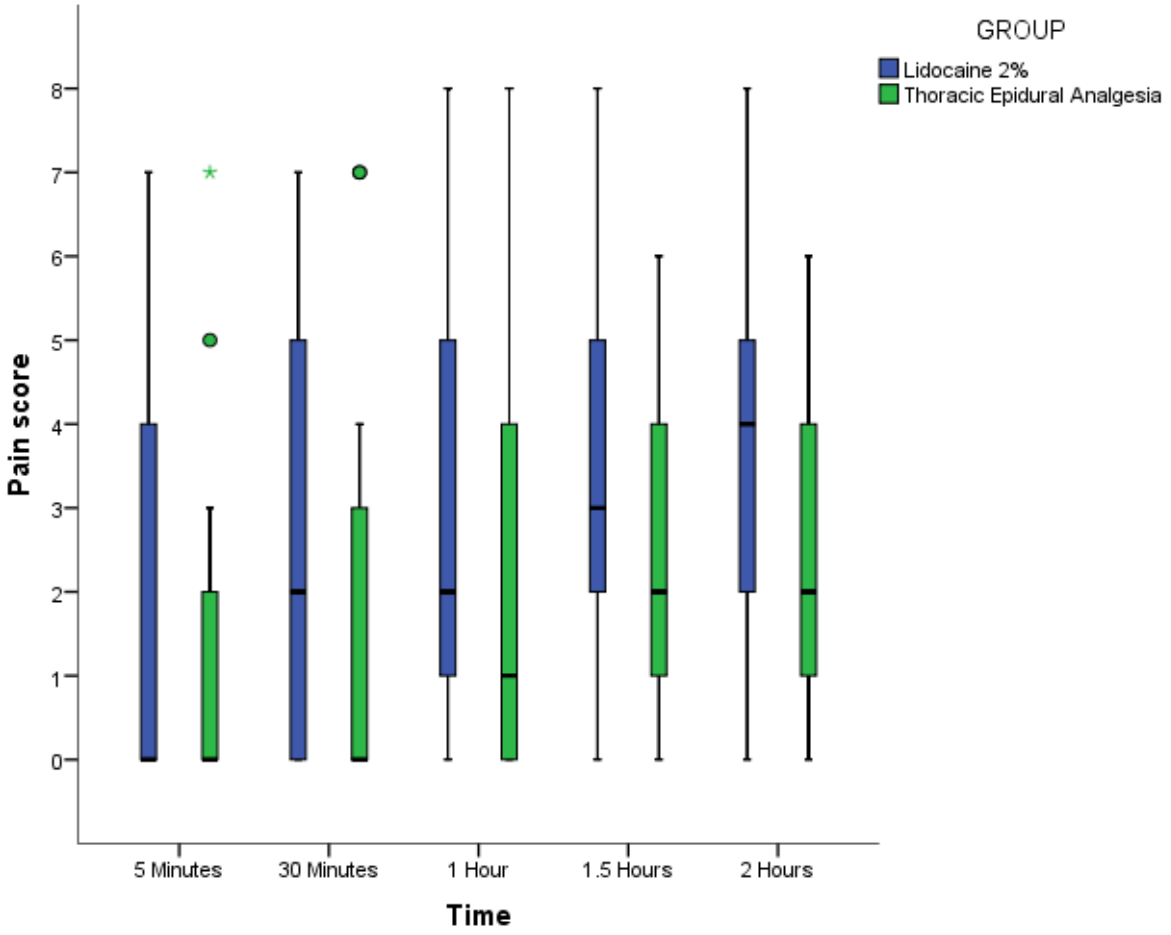


Figure 16: Pain score in both groups in the recovery room at 5 minutes of arrival, 30 minutes, 1 hour, 1.5 hours and 2 hours.

Table 8 : Comparison of baseline Pulse rate with postoperative pulse in the Post Anaesthesia Recovery Room

Parameter Pulse	Baseline	5 minutes	30 minutes	1 hrs	1.5 hrs	2 hrs
Group A (n = 19)	84.2 ± 10.9	84.1 ± 13.9	79.5 ± 12.9	80.2 ± 12.6	82.9 ± 16.1	82.4 ± 12.3
Group B (n = 16)	85.9 ± 11.1	78.7 ± 13.5	77.4 ± 12.9	81.7 ± 13.3	79.8 ± 12.6	79.8 ± 11.2
p - value	0.660	0.258	0.647	0.729	0.538	0.527

There was no significant change in the pulse rate in the immediate post operative period. Tachycardia is one of the signs of pain, when other causes like hypovolemia, blood loss and anxiety are eliminated.

Table 9 : Comparison of baseline Blood Pressure with postoperative values in Post Anaesthesia Recovery Room

Parameter Blood Pressure	Baseline	5 minutes	30minutes	1 hour	1.5 hrs	2 hrs
Group A SBP	130.3 ± 19.7	127.7 ± 17.1	129.1 ± 18.4	130.9±16.1	132.3±15.3	128.9±13.5
(n = 19) DBP	79.4 ± 7.9	74 ± 11.5	71.7 ± 10.5	77.9 ± 10.3	76.1 ± 10	74.6 ± 9.6
MAP	96.2 ± 10.2	91.6 ± 11.4	90.5 ± 12.1	95.2 ± 11.4	94.8 ± 10.5	92.7 ± 9.5
Group B SBP	132.4 ±13.6	132.3 ± 18.3	133.9 ± 16.9	131.4±20.6	126.4±17.1	127.6±13.6
(N = 16) DBP	80.9 ± 7.4	80.5 ± 12.1	79.0 ± 10.9	77.9 ± 11.9	76.7 ± 10.7	77.7 ± 9.4
MAP	98.2 ± 8.6	97.7 ± 13.3	97.4 ± 11.9	95.9 ± 13.8	93.3 ± 12.2	94.3 ± 9.8
p – value SBP	0.719	0.456	0.433	0.939	0.290	0.775
DBP	0.552	0.114	0.052	0.991	0.858	0.352
MAP	0.532	0.152	0.100	0.877	0.690	0.633

Blood pressure in the postoperative period was monitored in order to assess for any hypotension associated with either epidural or lidocaine infusion. Any rise in the blood pressure could have been due to anxiety or pain. However there was no statistically siginificant change in the blood pressure (systolic, diastolic and mean blood pressure) from the baseline measurement.

Table 10: Post - operative pain scores in the ward at various time intervals

Time	Arrival to ward	2 hrs	4hrs	8 hrs	12 hrs	24 hrs
Group A (mean±SD)	3.8 ± 3.0	4.4 ± 2.3	4.0 ± 2.4	3.3 ± 1.9	3.2 ± 1.9	2.9 ± 1.7
Group B (mean±SD)	2.8 ± 2.0	3.1 ± 2.4	2.4 ± 1.9	1.7 ± 1.7	1.6 ± 1.6	1.7 ± 1.5
p - value	0.260	0.134	0.047	0.018	0.015	0.043

Lidocaine group had a relatively higher number of patients in the moderate pain score category as compared to the TEA group, as seen in the table. All the pain scores in both groups, however, were less than 5. The pain scores were measured at arrival to the surgical ward and at 2, 4, 8, 12, 24 hours postoperative.

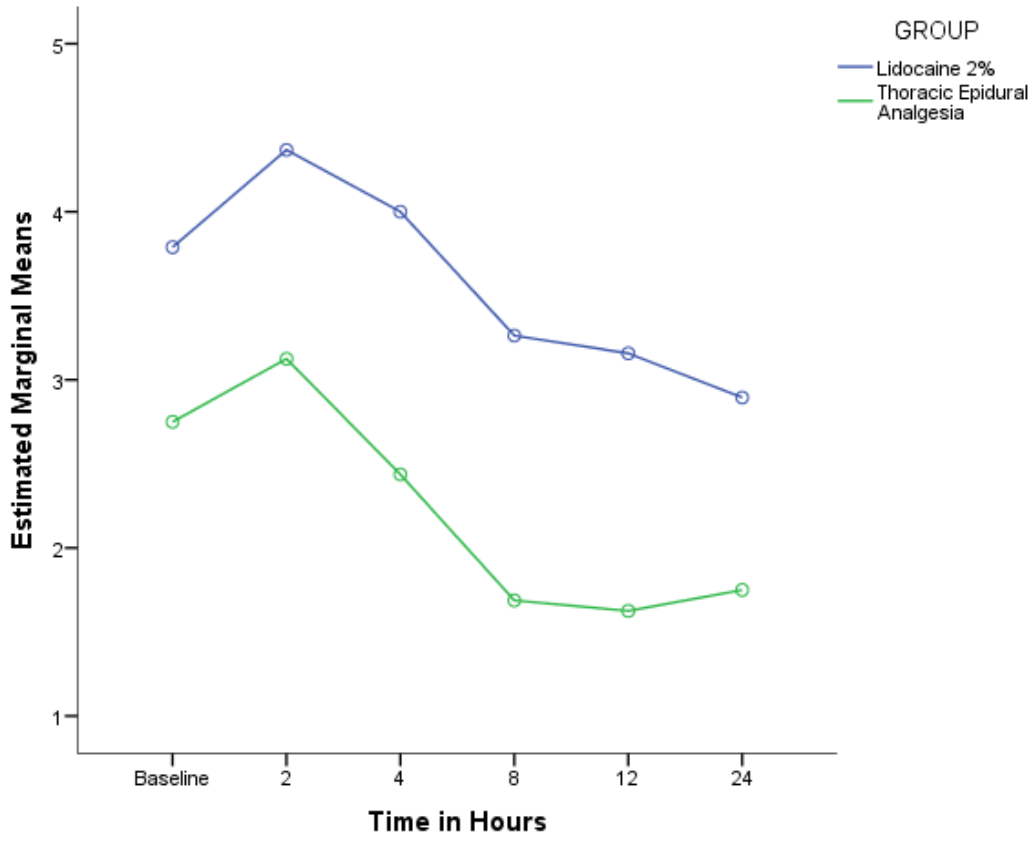


Figure 17 : Comparison of postoperative pain scores at various time intervals.

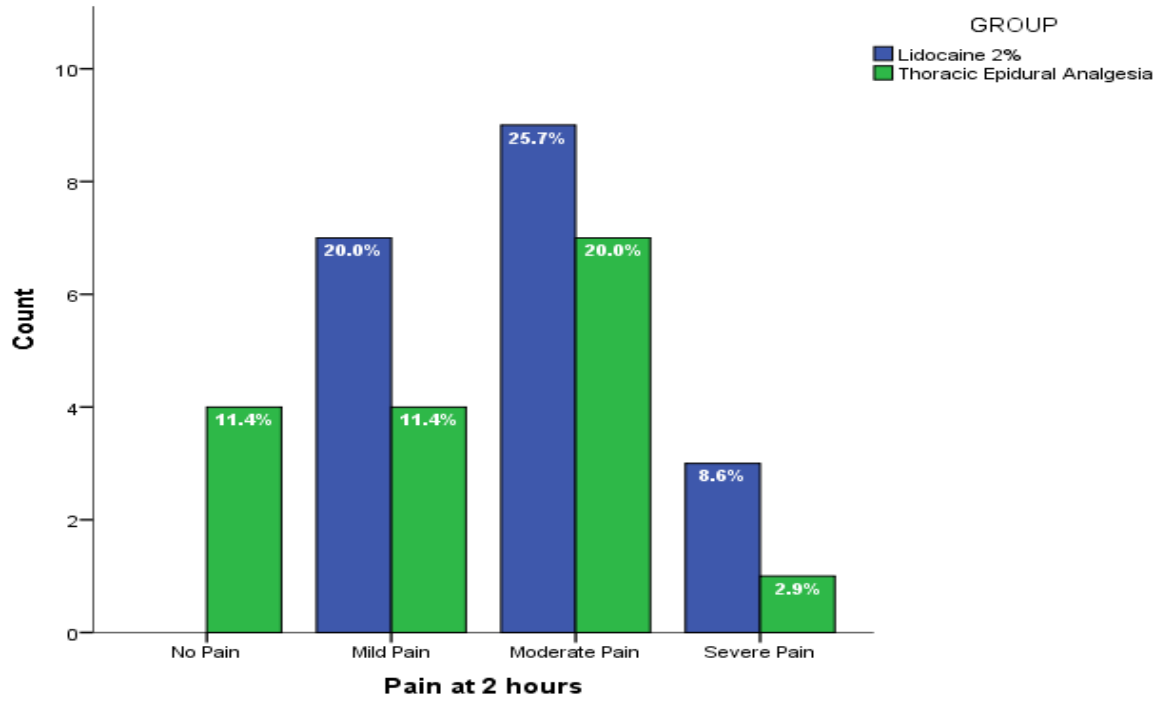


Figure 18 : NRS scores at 2 hours post arrival to ward.

8.6% of patients in the lidocaine group had severe pain at 2 hours as compared to 2.9% of patients in TEA (NRS scores 7 – 10) . 25.7% in group A and 20 % in group B had moderate pain (NRS 4 -6). The rest of the patients had a score of < 4. The p value is 0.134, and hence there is no statistical significance between the two groups.

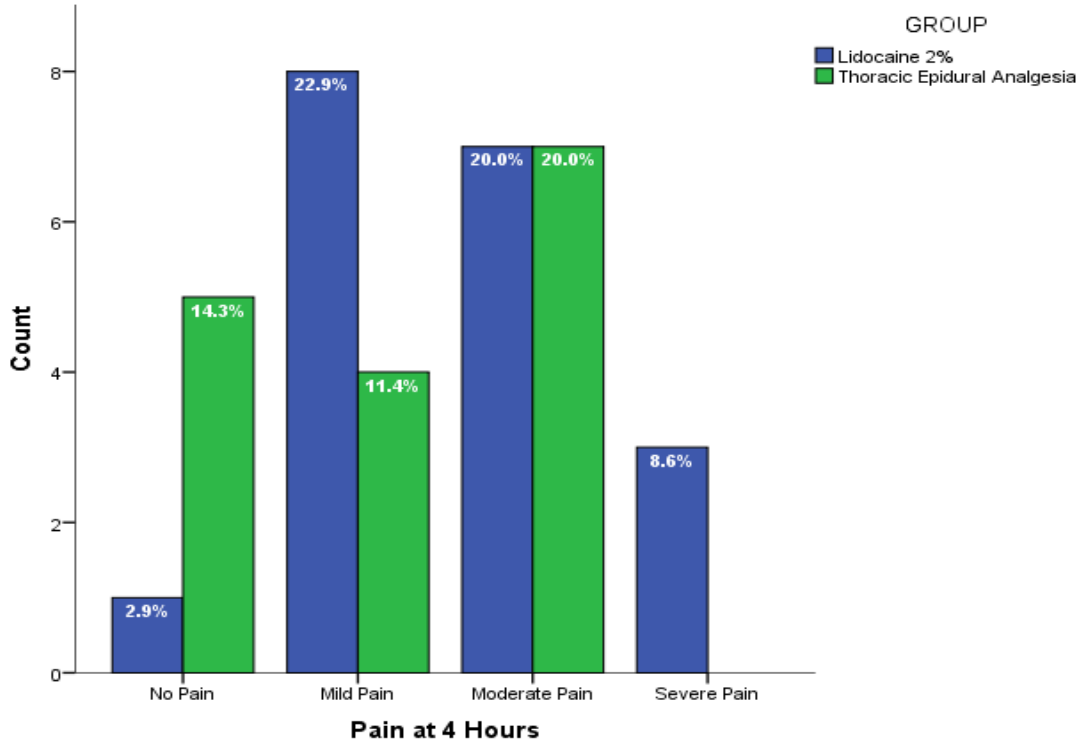


Figure 19: NRS at 4 hours in the ward; 22.9 % of the patients in group A and 11.4% of patients in group B had mild pain (NRS 1 - 3), but 20% of the patients in both the groups had moderate pain at 4 hours. 8.6% in Group A and none in group B had severe pain (NRS 7 - 10); p value – 0.047, there was a significantly higher pain score at 4 hours in group A.

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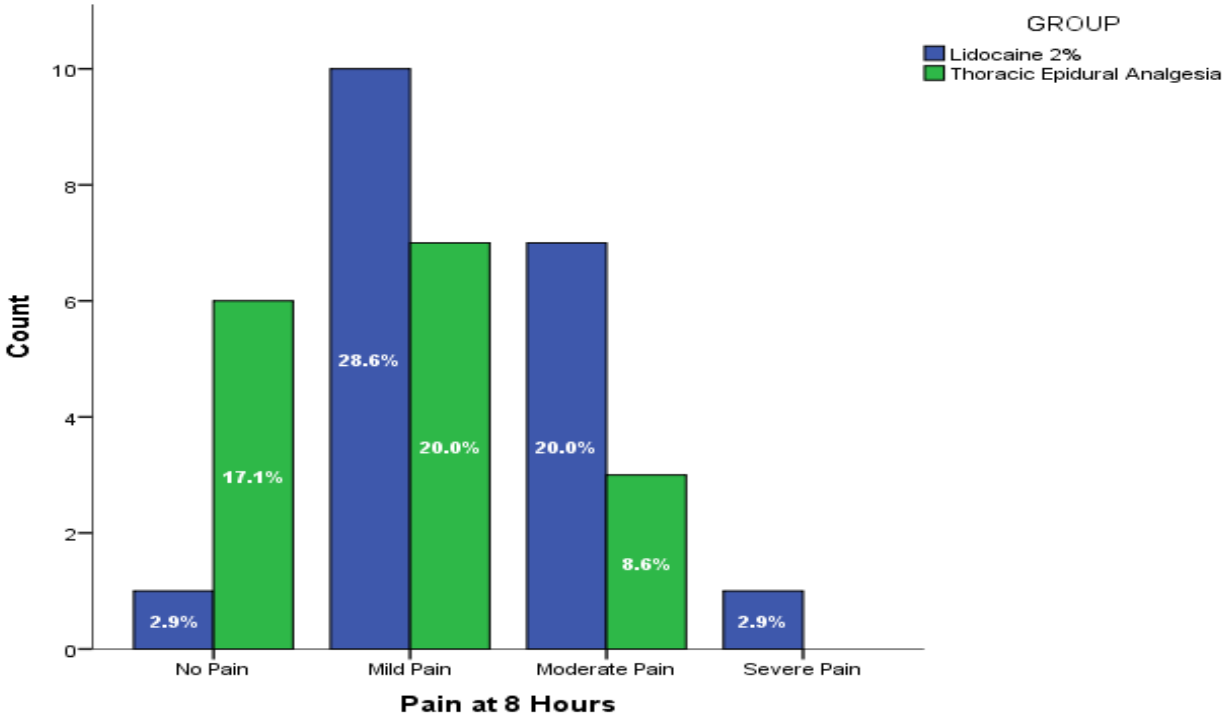


Figure 20: NRS at 8 hours in the ward; 28.6% of patients in group A and 20% in group B had mild pain and 20% in group A and only 8.6% in group B had moderate pain. 2.9% in group A also had severe pain; p value is 0.018 and hence the difference is statistically significant.

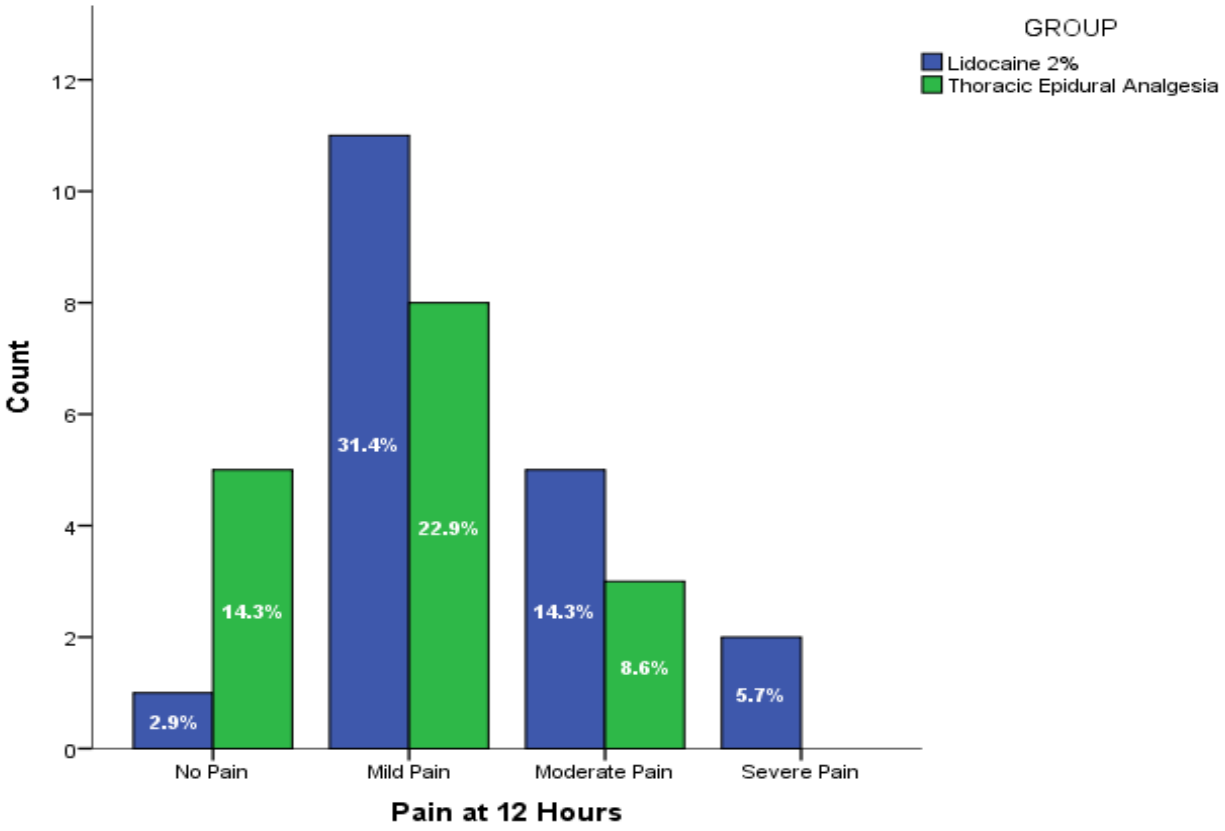


Figure 21: NRS at 12 hours in the ward; 31.1% of patients in group A and 22.9% in group B had mild pain at 12 hours. 14.3% in group A versus 8.6% in group B had moderate pain whereas 5.7% of patients in group A had severe pain. The p value is 0.015 and hence clinically significant.

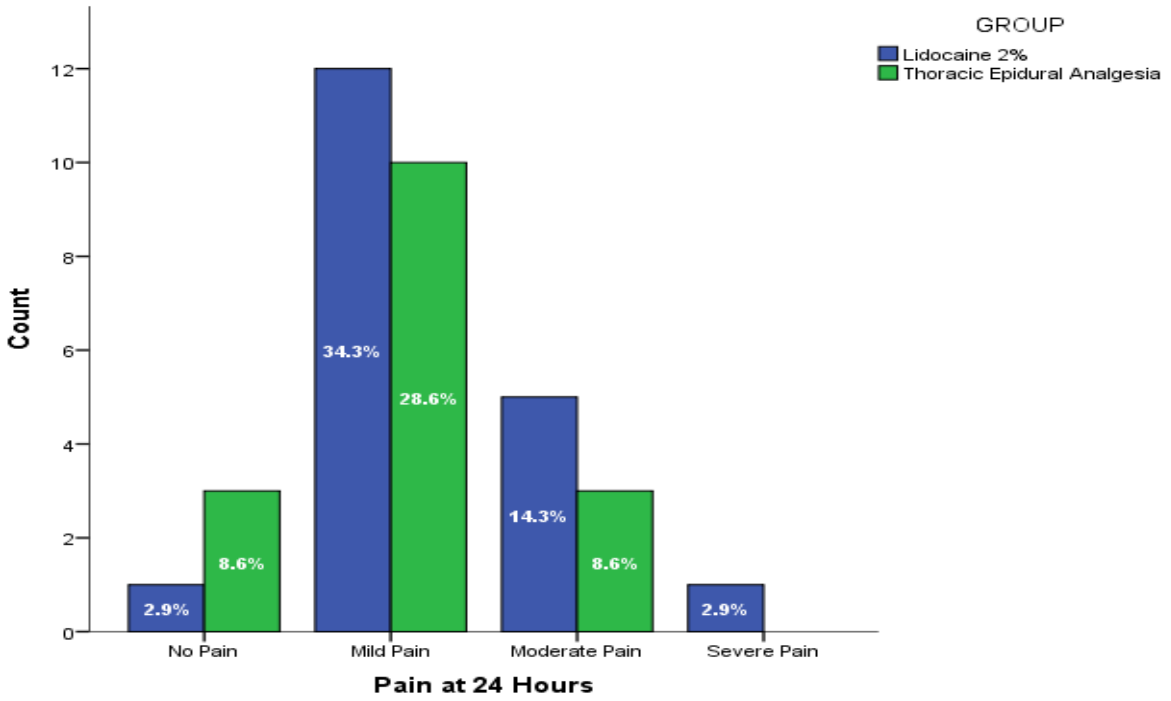


Figure 22: NRS at 24 hours in the ward; 34.3% in group A and 28.6% in group B had mild pain at 24 hours. 14.3% in group A and 8.6% in group B had moderate pain. 2.9% in group A complained of severe pain. The p value is 0.043 and hence statistically significant.

Table 11: Total amount of PCA Fentanyl used in the post – operative ward

Parameter Time interval	Group A Lidocaine (N=19) (micrograms)	Group B TEA (N = 15) (micrograms)	P value
Arrival to 2 hrs	67.4 ± 35.4	29.3 ± 45.9	0.010
2 – 4 hrs	75.8 ± 43	28 ± 39.9	0.002
4 – 8 hrs	63.2 ± 52.2	38.7 ± 47.5	0.167
8 -12 hrs	79 ± 56	30.7 ± 45.3	0.011
12 -24 hrs	79 ± 61	38.7 ± 33.4	0.028

The postoperative opioid requirement is one of the secondary outcomes of the study. Each patient received a patient demand based PCA (CADD) pump which was preloaded with Fentanyl at 20 mcg/ml. The lockout time was 15 minutes without any background infusion. The CADD pump was checked for the number of doses delivered to the patient at arrival and at 2, 4, 8, 12, 24 hours post discharge from the post anaesthesia care room to the surgical ward. The total dose of fentanyl consumed was then calculated based on the number of CADD pulses.

This was the only opioid administered to the patient in the postoperative period and hence gives an exact value for requirement of opioids in the postoperative period. The

mean number of times the CADD pump dose was delivered at the said intervals was compared between the two arms using two independent sample t test.

One patient in the TEA group had severe pain (NRS - 10) in the postoperative ward. The sensory level achieved was inadequate, not relieved by readjusting the catheter or by repeated epidural boluses. Hence it was decided by the anaesthetist to start a low dose morphine continuous infusion (Dosifuser) over 24 hours. Hence, 15 patients were analysed in Group B for this variable.

The mean PCA – fentanyl dose used by the Lidocaine group was noticed to be significantly higher than the amount used by the TEA group during the following time intervals – from arrival to ward (p value – 0.010), from 2 – 4 hours (p value – 0.002), from 8 -12 hours (p value – 0.011) and 12 – 24 hours (p value – 0.028).

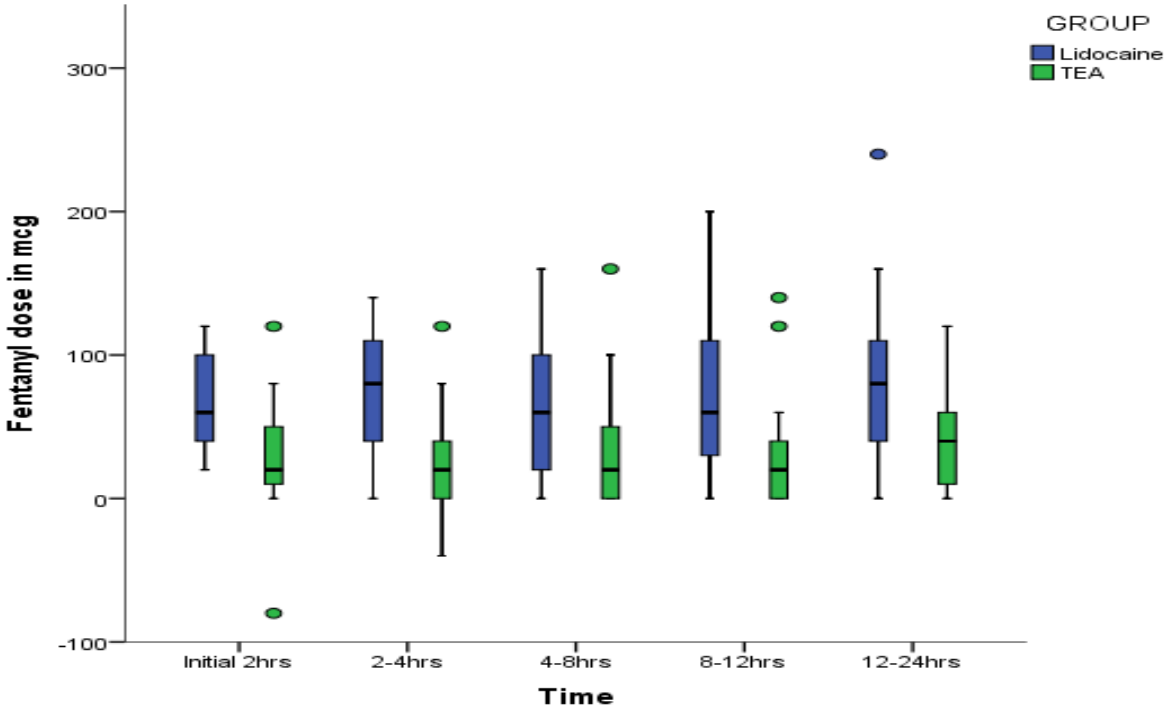


Figure 23: PCA – Fentanyl consumption at different time intervals

Table 12 : Quality of Recovery Score (QoR) – 15

Parameters	Group A IV Lidocaine (N=19)	Group B TEA (N=16)	P value
Pre op QoR score	142.3 ± 10.9	142.8 ± 10.6	0.906
Post op QoR score	124.9 ± 21.7	121.2 ± 20.1	0.601
Percentage change	11.6%	14.4%	0.508

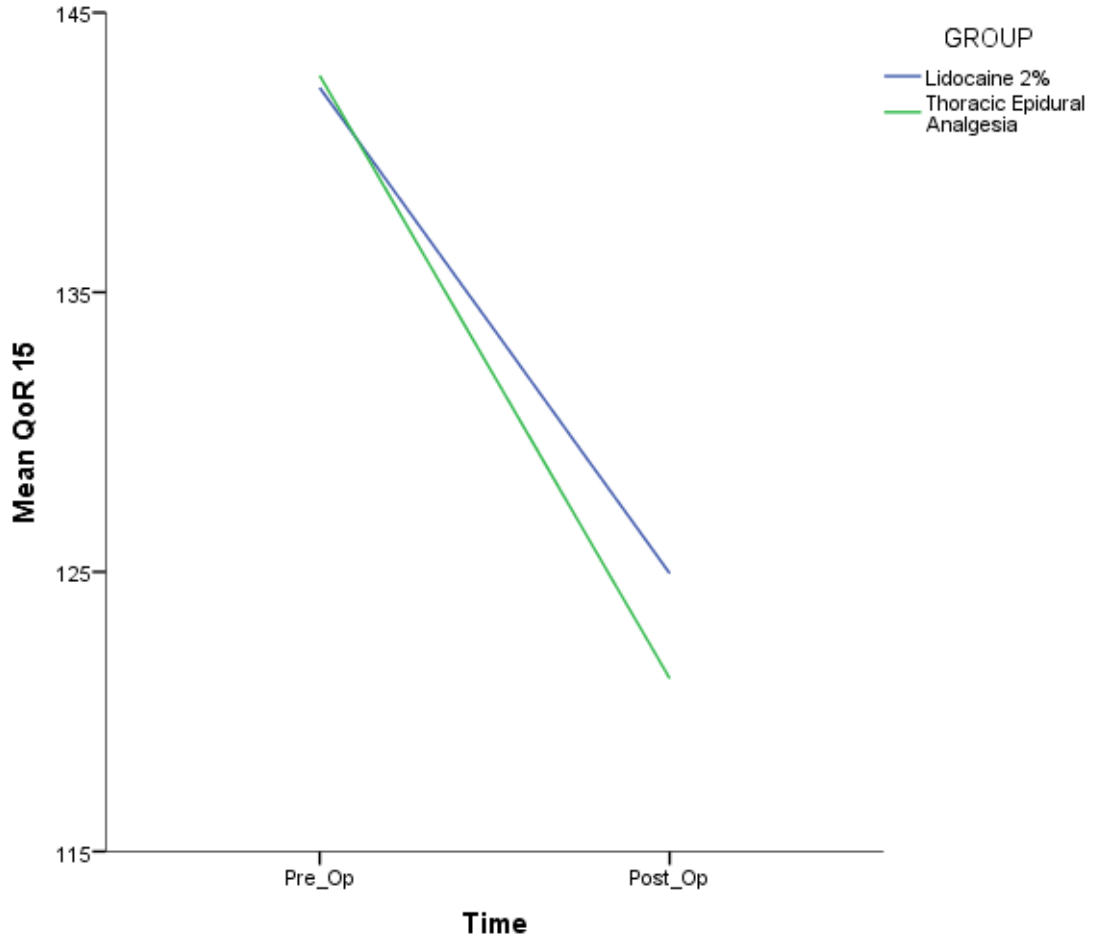


Figure 24 : Comparison of preoperative QoR score with Postoperative QoR score

Many scales for rating the quality of recovery have been developed, but QoR - 15, a fifteen - item questionnaire is used in the study as it provides a comprehensive score that covers five dimensions of recovery – patient comfort, emotional state, physical dependence, patient support and pain. It is derived from the QoR – 40 questionnaire, which is a set of 40 questions covering the said dimensions and hence more time consuming. QoR – 15, on the other hand, can be completed in 3 – 5 minutes.

QoR - 15 scores range from 0 to 150, representing worst quality of recovery and excellent quality of recovery, respectively. One of the secondary outcomes of the study was to find out which group had a better quality of recovery.

The quality of recovery QoR – 15 score was analysed as the difference in the total scores between the two groups and the preoperative baseline score was compared with the postoperative score.

The baseline QoR score was taken one day prior to the surgery. Both Lidocaine and TEA group had a similar baseline score, 142.3 ± 10.9 versus 142.8 ± 10.6. The mean time of assessment of the postoperative score was 37 h after surgery, range 31– 44 h (p value – 0.700). The postoperative score for Lidocaine group was 124.9 ± 21.7 and 121.2 ± 20.1 for TEA group. The percentage change between preoperative and postoperative QoR score in Lidocaine group is ***11.6%*** and ***14.4 %*** in TEA group. Even though lidocaine group showed higher scores and hence a better quality of recovery as compared to the TEA group, it was not statistically significant since p value was 0.601.

Table 13: Comparison of Components of QoR – 15 score between Group A and Group B

QoR – 15 Parameters		Preoprative	Postoperative
Able to breathe easy	A : Lidocaine	9.7 ± 0.7	9.5 ± 1.0
	B : TEA	10 ± 0.0	9.4 ± 1.4
Been able to enjoy food	A : Lidocaine	9.8 ± 0.4	7.9 ± 2.9
	B : TEA	9.3 ± 1.6	6.7 ± 2.7
Feeling rested	A : Lidocaine	9.0 ± 1.9	7.8 ± 2.3
	B : TEA	9.2 ± 1.4	8.6 ± 1.6
Have had a good sleep	A : Lidocaine	9.3 ± 1.4	8.4 ± 1.9
	B : TEA	8.9 ± 2.1	7.7 ± 1.9
Able to look after personal toilet and hygiene unaided	A : Lidocaine	9.6 ± 0.9	8.0 ± 2.6
	B : TEA	10 ± 0.0	6.6 ± 3.3
Able to communicate with Family or friends	A : Lidocaine	9.9 ± 0.2	9.7 ± 0.8
	B : TEA	10 ± 0.0	9.2 ± 2.0
Getting support from hospital doctors and nurses	A : Lidocaine	9.9 ± 0.2	9.8 ± 0.6
	B : TEA	10 ± 0.0	9.4 ± 1.6
Able to return to work or usual home activities	A : Lidocaine	9.4 ± 1.0	7.1 ± 2.6
	B : TEA	9.9 ± 0.3	6.9 ± 2.9
Feeling comfortable and in Control	A : Lidocaine	9.5 ± 1.4	8.3 ± 2.1
	B : TEA	9.7 ± 0.6	7.9 ± 1.8
Having a feeling of general well-being	A : Lidocaine	9.3 ± 1.5	8.3 ± 2.1
	B : TEA	9.6 ± 0.7	8.4 ± 1.6
Moderate pain	A : Lidocaine	8.9 ± 1.5	6.5 ± 2.0
	B : TEA	8.9 ± 0.8	7.3 ± 1.8
Severe pain	A : Lidocaine	9.9 ± 0.2	8.7 ± 2.4
	B : TEA	9.6 ± 1.5	9.4 ± 2.3
Nausea or vomiting	A : Lidocaine	10 ± 0.0	8.4 ± 3.0
	B : TEA	9.6 ± 1.2	6.9 ± 3.2
Feeling worried or anxious	A : Lidocaine	8.5 ± 2.1	7.8 ± 2.7
	B : TEA	8.9 ± 1.9	8.6 ± 1.4
Feeling sad or depressed	A : Lidocaine	8.9 ± 2.0	8.7 ± 1.9
	B : TEA	9.0 ± 1.5	8.9 ± 1.4
Total	A : Lidocaine	142.3 ± 10.9	124.9 ±21.7
	B : TEA	142.8 ± 10.6	121.2±20.1

Table 14 : Time of hospital discharge

Parameters	Mean	SD
Group A : IV Lidocaine (N=19)	9.3	7.9
Group B : TEA (N=16)	8.4	3.8

The average time of discharge was at post operative day 9 for group A (9.3 ± 7.9) and 8 (8.4 ± 3.8) for group B. There was no significant difference in the duration of hospital stay in both groups ; p value – 0.678.

63.2% patients in group A versus 53.3% of the patients in group B stayed in the hospital for < 7 days, whereas 36.8% in group A and 46.7% in group B stayed for >7 days in the hospital. Even though Group A (lidocaine) appears to be associated with lesser duration of hospital stay when compared to group B (TEA), the difference is not statistically significant ; p value – 0.563.

DISCUSSION

Our randomized trial compared the efficacy of continuous intravenous infusion of 2% lidocaine in Laparoscopic colorectal surgery with the standard of thoracic epidural analgesia for post operative analgesia.

Both groups comprised of patients who were matched with regard to age - group A - 47.7 ± 15.8 (mean ± SD) versus group B - 51.1 ± 12.4; p – 0.492 . There was no difference in the gender distribution. Male : Female (M: F) ratio was – group A - 13 (68.4%): 6 (31.6%) and group B - 11 (68.8%): 5 (31.2%), p – 0.983. The distribution of comorbidties and ASA risk status had no significant variation either. TEA group had a significant number of patients with a lower body mass index as compared to Lidocaine group; group A – 25.5 (4.0) versus 23 (2.7), $p < 0.05$. Both arms were matched at baseline vital parameters.

Surgical factors such as duration of surgery, type of surgical resection performed and the duration of anaesthesia given were comparable in both the groups.

Our primary outcome was to see if the use of intaoperative lidocaine infusion translated to adequate pain relief in the immediate postoperative period. The secondary outcome was to compare the quality of recovery, the duration of hospital stay and to ascertain the degree of known side effects of said modes of analgesia in laparoscopic colorectal surgeries.

Numerical Rated Scores for post operative pain was assessed on arrival to the postoperative care unit and then assessed half hourly for a total of 2 hours. Lidocaine (Group A) was allocated a total of 19 patients and TEA (Group B) had 16 patients. The projected number for a power of 80 was 18 in each arm. However 24 patients

were intended to be included in each arm for a power of 90, but during the study period, the total number of patients coming for the procedure had significantly decreased due to various reasons.

The NRS in the study arm had slightly higher mean (SD) pain scores - 1.8(2.4), 2.4(2.5), 3.2(2.8), 3.4(2.6), 3.5(2.5) compared to the control arm - 1.1(2.1), 1.5(2.5), 2.1(2.7), 2.2(1.8), 2.2(1.9) at 5 minutes, 30, 60, 90 minutes and 2 hours after arrival to PACU. There was no statistically significant difference between the arms.

The NRS among the two arms recorded at arrival to the inpatient ward and at 2, 4, 8, 12 and 24 hours shows mean(SD) in Lidocaine arm 3.8(3.0), 4.4(2.3), 4.0(2.4), 3.3(1.9), 3.2(1.9), 2.9(1.7) and in the Thoracic epidural group 2.8(2.0),3.1(2.4),2.4(1.9),1.7(1.7),1.6(1.6),1.7(1.5). The pain score in the lidocaine group was 1 – 1.5 times higher than the TEA group and the difference was significant ($p < 0.05$) from the 4^{th} hour onwards. As demonstrated by Staikou (120) et al, who compared the effects of intravenous lidocaine (1.5 mg/kg bolus, 2 mg/kg/h infusion) with continuous epidural lidocaine till the end of the surgery, the analgesic effect of intravenous lidocaine was comparable to epidural lidocaine, and this effect was evident in the early postoperative period, especially in the 1^{st} hour and it gradually reduced subsequently. This was attributed to the use of low dose intravenous doses which was probably subtherapeutic for prolonged analgesic effects. Break through pain was treated with the intravenous Fentanyl bolus delivered by PCA pump. The use of fentanyl at 2, 4, 8, 12 and 24 hours in Group A (Lidocaine) were 67.4(35.4), 75.8(43), 63.2(52.2), 79(56), 79(61) - mean in microgram(SD). Group B (Epidural) used 29.3(45.9), 28(39.9), 38.7(47.5), 30.7(45.3) and 38.7(33.4) - mean(SD) in

micrograms. Fentanyl usage between the two arms was significantly higher in group A at 2,4,12 and 24 hours ($p < 0.05$). The utilization of fentanyl for break through pain was higher in the study arm at all points of recording. Though the NRS in the study arm was not significantly higher for the first 4 hours, the data on the fentanyl use reveals a significantly higher use in this arm. The continued higher demand for fentanyl for analgesia from 4 to 24 hours with concomitant higher pain scores in the study arm may be explained by the longer than usual lock out period of 15 minutes in the PCA pump. All patients received regular intravenous paracetamol at 20mg/Kg on a 6 hourly basis.

The early onset of break through pain in the lidocaine infusion is due its shorter duration of action (120 – 160 minutes). Also, the loading dose and infusion concentration may not have been adequate for our study population. Thoracic epidural, because of its continuous delivery will continue to prevent supraspinal sensitization and thus decreasing the perception of pain.

The study also looked at the following secondary outcomes: Quality of recovery scores using a 15 point questionnaire which was compared preoperatively and post operatively. In group A, preoperative score was 142.3 (10.9) and postoperative score was 124.9 (21.7) with a change of 11.6%, group B had a preoperative score of 142.8 (10.6) and a postoperative score of 121.2 (20.1) with a percentage change of 14.4%. There was no significant difference in the quality of recovery between both the arms ($p < 0.05$).

Both lidocaine infusion and TEA have been known to attenuate pain response intraoperatively and provide adequate postoperative pain relief in open abdominal surgeries (23,121). These techniques are also part of the evidence - based fast track surgical protocols such as ERAS (Enhanced Recovery After Surgery) guidelines, a multimodal protocol that requires a multidisciplinary team which is focused on reduction of perioperative stress, thus facilitating improved surgical outcomes distinctively in patients undergoing colorectal resections. The said protocol is aimed at reducing the duration of hospital stay and therefore the associated hospitalization expenditure and also at attenuating the rate of postoperative complications such as paralytic ileus, anastomotic leaks and sepsis.

But the scope of lidocaine infusion versus TEA in laparoscopic surgeries for postoperative analgesia is still under debate. The pain associated with laparoscopic surgeries is largely undermined and inadequately treated. Ekstein et al (5) demonstrated that the pain in the first 4 hours post laparoscopic surgery is much more than the pain experienced post laparotomy and the pain and analgesic requirement is as much as laparotomy patients in the first 24 hours. However, there was a consistent reduction in pain intensity in the laparoscopic group after the initial 24 hours and hence associated with better outcomes.

Pain perception is an extremely subjective variable which has complex multifactorial central and peripheral neural mechanisms and whether it is possible to objectively quantify it is still debatable (122). However we have used the NRS scoring to determine pain intensity which is currently one of the most valid scores to assess pain (123).

Our data revealed results similar to the previous studies as most of the patients had mild to moderate pain (NRS 1-3 and 4-6 respectively) and few of them had severe pain (NRS 7 - 10) at various time points over the first 24 hours. The mean pain scores were lower in the epidural group than lidocaine at 2, 4, 8, 12 and 24 hours. Most of the patients had scores between NRS 1- 3 in TEA and NRS 4-6 in lidocaine group.

In our study, Lidocaine was administered as a bolus injection (2mg/kg) followed by an infusion (2mg/kg/hr) which was continued till 30 minutes post extubation. According to Kranke (23), lidocaine infusion dose of ≥ 2 mg/kg/h demonstrated an evidence of effect for reduced pain intensity when compared to doses < 2mg/kg/h, which did not demonstrate any evidence of effect. Also Eipe et al (121) demonstrated that a dose of 1 – 2 mg/kg/hr leads to plasma levels of <5mcg/mL. Previous studies have used various dosage regimens of lidocaine intra and postoperatively and have demonstrated adequate analgesia during and even after stopping the infusion which have been attributed to its analgesic and anti – inflammatory property which is known to decrease the release of cytokines both in vitro and in vivo by inhibiting neutrophil activation (7,62,77) that persists even after reduced plasma levels. Khan et al (124), in their meta-analysis, concluded that there is no additional benefit of continuing intravenous lidocaine infusion beyond 60 minutes of surgical closure as the effects are known to last for 72 hours after stopping the infusion.

Though the intraoperative analgesic consumption was comparable in both the study groups, suggesting adequate levels of analgesia, our data shows that during the postoperative period, analgesic requirement in the TEA group was lower than

lidocaine group. The amount of PCA fentanyl used by TEA group was almost half the amount used by lidocaine group over 24 hours.

However, the quality of recovery score was marginally higher in lidocaine group (124.9 ± 21.7 versus 121.2 ± 20.1, p value - 0.601) which does not correlate with the increased PCA use by the lidocaine group. It may be possible that patients were not completely well versed in the handling of PCA, which might have resulted in its increased usage.

The mean duration of hospital stay for Lidocaine group was 9.3 (7.9) and for TEA group was 8.4 (3.8) days, demonstrating a lack of significant difference between the two groups (p value – 0.678).

Lidocaine group had 5 patients who complained of abdominal distension which was conservatively managed. There was one patient who developed postoperative anastomotic leak and abscess formation requiring a redo laparotomy and ICU admission for stabilisation. There were no intraoperative or postoperative adverse effects that were directly related to the toxicity of lidocaine. The higher number of paralytic ileus in this study arm could be because of the increased use of fentanyl. 1 patient had new onset premature ventricular complexes in the intraoperative period, which was suspected to be the result of PICC (Peripherally Inserted Central Catheter) line, and which resolved after the catheter was pulled out by a few centimetres.

TEA group also had two patients who complained of postoperative ileus and severe vomiting, one patient who was diagnosed with a contained leak and was managed conservatively. One patient underwent redo laparotomy for anastomotic leak and

pelvic abscess drainage and required inotropic support and ICU care. 1 patient had catheter displacement in the postoperative ward requiring readjustment and one patient had severe pain in the immediate postoperative period requiring morphine dosifuser. 2 patients did not have an adequate sensory level.

Even though TEA appears to be superior to lidocaine infusion in controlling postoperative pain, there was no clinically significant difference in the quality of recovery and hospital stay among both the groups. Keeping in mind the challenges associated with TEA, it appears that lidocaine could benefit as an alternative mode of postoperative analgesia, which not only has opioid sparing effect but is also cost-effective.

IMPLICATION FOR FUTURE RESEARCH

Majority of the studies that were reviewed administered 1- 2mg/kg of lidocaine as a bolus and infusion. The most adequate dose and duration of the administration of lidocaine for analgesia and anti – inflammatory property in various types of surgeries is still indefinite. Further studies involving larger sample size with different dosing regimens will need to be studied to identify the correct dose and correlate its clinical efficacy, if any.

More research in the paediatric age group, patients with renal and hepatic dysfunction are needed to quantify the pertinent dosages.

LIMITATIONS

This study was underpowered to obtain a significant difference and hence a greater insight into the secondary outcomes.

Surgical and anaesthetic experience was not factored into the study, due to heterogenous surgical and anaesthetic team involved.

Previous abdominal surgeries and the location and invasion of the tumors which are likely to increase the surgical technical difficulty and hence greater pain scores were not factored into the study.

Patient understanding of the use of the PCA pump could have affected its use in the ward, thus giving a false high or low analgesic consumption.

The single centre RCT confers a certain level of bias, which needs to be allayed through a well-constructed multi - centered RCT.

Lidocaine infusion was delivered only till 30 minutes post surgery which warrants further research into the effects of its continuous infusion for 12 – 24 hours postoperative to extract additional information such as the change in requirement for further analgesia, time taken for ambulation, incidence and correlation of postoperative ileus and anastomotic leaks, dose dependent effects and the effect on duration of discharge which could have been analysed and compared with the TEA group. Further titration of the dose regimen using measurement of plasma lidocaine

levels for toxicity is needed to establish a safe dosage for adequate analgesia as lidocaine has a relatively narrow therapeutic index.

Thus there is a potent indication to treat laparoscopic patients aggressively in the initial postoperative period to improve patient satisfaction and overall quality of recovery

CONCLUSION

Thoracic epidural analgesia is associated with better pain relief, lower intensity of postoperative pain at various time points in the first 24 hours, reduces the postoperative analgesic requirement as compared to patients who received lidocaine infusion in all patients undergoing elective laparoscopic colorectal surgeries. However, both lidocaine and TEA have comparable effects on the overall quality of recovery and duration of hospital stay and without any major adverse effects. Thus the use of intravenous lidocaine as an inexpensive, convenient and safe modality which can potentially be used as an alternative mode of perioperative, non - opioid analgesia cannot be ruled out.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012: Global Cancer Statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87–108.

2. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. The Lancet. 2003 Dec 6;362(9399):1921–8.

3. Impact of Operative Duration on Postoperative Pulmonary Complications in Laparoscopic vs Open Colectomy - SAGES Abstract Archives [Internet]. SAGES. [cited 2018 Aug 6]. Available from: https://www.sages.org/meetings/annual-meeting/abstracts-archive/impact-of-operative-duration-on-postoperative-pulmonary-complications-in-laparoscopic-vs-open-colectomy/

4. Barr J, Boulind C, Foster JD, Ewings P, Reid J, Jenkins JT, et al. Impact of analgesic modality on stress response following laparoscopic colorectal surgery: a post-hoc analysis of a randomised controlled trial. Tech Coloproctology. 2015 Apr;19(4):231–9.

5. Ekstein P, Szold A, Sagie B, Werbin N, Klausner JM, Weinbroum AA. Laparoscopic Surgery May Be Associated With Severe Pain and High Analgesia Requirements in the Immediate Postoperative Period: Ann Surg. 2006 Jan;243(1):41–6.

6. Garimella V, Cellini C. Postoperative Pain Control. Clin Colon Rectal Surg. 2013 Aug 19;26(03):191–6.

7. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, et al. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. Br J Anaesth. 2006 Nov;97(5):640–6.

8. Liu S, Carpenter RL, Neal JM. Epidural Anesthesia and AnalgesiaTheir Role in Postoperative Outcome. Anesthesiol J Am Soc Anesthesiol. 1995 Jun 1;82(6):1474-1506.

9. Rimback G, Cassuto J. Treatment of Postoperative Paralytic Ileus by Intravenous Lidocaine Infusion. ANESTH ANALG. :6.

10. Pöpping DM. Protective Effects of Epidural Analgesia on Pulmonary Complications After Abdominal and Thoracic Surgery: A Meta-Analysis. Arch Surg. 2008 Oct 20;143(10):990.

11. Christie IW, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey: Epidural complications. Anaesthesia. 2007 Mar 21;62(4):335–41.

12. Marret E, Remy C, Bonnet F. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. BJS. 2007 Jun 1;94(6):665–73.

13. Levy BF, Scott MJ, Fawcett W, Fry C, Rockall TA. Randomized clinical trial of epidural, spinal or patient-controlled analgesia for patients undergoing laparoscopic colorectal surgery. Br J Surg. 2011 Aug;98(8):1068–78.

14. Tauzin-Fin P, Bernard O, Sesay M, Biais M, Richebe P, Quinart A, et al. Benefits of intravenous lidocaine on post-operative pain and acute rehabilitation after laparoscopic nephrectomy. J Anaesthesiol Clin Pharmacol. 2014 Jul 1;30(3):366.

15. Grady P, Clark N, Lenahan J, Oudekerk C, Hawkins R, Nezat G, et al. Effect of intraoperative intravenous lidocaine on postoperative pain and return of bowel function after laparoscopic abdominal gynecologic procedures. AANA J. 2012 Aug;80(4):282–8.

16. Koppert W, Weigand M, Neumann F, Sittl R, Schuettler J, Schmelz M, et al. Perioperative Intravenous Lidocaine Has Preventive Effects on Postoperative Pain and Morphine Consumption After Major Abdominal Surgery: Anesth Analg. 2004 Apr;1050–5.

17. Hollmann MW, Durieux ME. Local Anesthetics and the Inflammatory ResponseA New Therapeutic Indication? Anesthesiol J Am Soc Anesthesiol. 2000 Sep 1;93(3):858–75.

18. Herroeder S, Pecher S, Sch??nherr ME, Kaulitz G, Hahnenkamp K, Friess H, et al. Systemic Lidocaine Shortens Length of Hospital Stay After Colorectal Surgery: A Double-blinded, Randomized, Placebo-controlled Trial. Ann Surg. 2007 Aug;246(2):192–200.

19. De Oliveira GS, Fitzgerald P, Streicher LF, Marcus R-J, McCarthy RJ. Systemic Lidocaine to Improve Postoperative Quality of Recovery After Ambulatory Laparoscopic Surgery: Anesth Analg. 2012 Aug;115(2):262–7.

20. Durieux ME. The Poor Man's Epidural: Systemic Local Anesthetics and Surgical Outcomes. :2.

21. Tikuišis R, Miliauskas P, Samalavičius NE, Žurauskas A, Samalavičius R, Zabulis V. Intravenous lidocaine for post-operative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. Tech Coloproctology. 2014 Apr;18(4):373–80.

22. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis † †This review is an abridged version of a Cochrane Review previously published in the

Cochrane Database of Systematic Reviews 2015, Issue 7, DOI: CD009642 (see www.thecochranelibrary.com for information).1 Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. Br J Anaesth. 2016 Jun;116(6):770–83.

23. Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Anaesthesia, Critical and Emergency Care Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Jul 16 [cited 2018 Jul 18]; Available from: http://doi.wiley.com/10.1002/14651858.CD009642.pub2

24. Wongyingsinn M, Baldini G, Charlebois P, Liberman S, Stein B, Carli F. Intravenous lidocaine versus thoracic epidural analgesia: a randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program. Reg Anesth Pain Med. 2011 Jun;36(3):241–8.

25. Swenson BR, Gottschalk A, Wells LT, Rowlingson JC, Thompson PW, Barclay M, et al. Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. Reg Anesth Pain Med. 2010 Aug;35(4):370–6.

26. Lignocaine Injection [Internet]. Pfizer: the world's largest research-based pharmaceutical company. 2016 [cited 2018 Aug 11]. Available from: https://www.pfizer.com.au/products/lignocaine-injection

27. XYLOCAINE_INJECTION-PI.pdf.

28. Giovannitti JA, Rosenberg MB, Phero JC. Pharmacology of Local Anesthetics Used in Oral Surgery. Oral Maxillofac Surg Clin N Am. 2013 Aug;25(3):453–65.

29. Gordh T, Gordh TE, Lindqvist K. Lidocaine: The Origin of a Modern Local Anesthetic: Anesthesiology. 2010 Dec;113(6):1433–7.

30. Holmdahl MH. Xylocain (lidocaine, lignocaine), its discovery and Gordh's contribution to its clinical use. Acta Anaesthesiol Scand Suppl. 1998;113:8–12.

31. Gordh T. XYLOCAIN?A NEW LOCAL ANALGESIC. Anaesthesia. 1949 Mar;4(1):4–9.

32. Gordh T, Gordh TE, Lindqvist K. Lidocaine: The Origin of a Modern Local Anesthetic. Anesthesiol J Am Soc Anesthesiol. 2010 Dec 1;113(6):1433–7.

33. WHO Essential Medicines List | UICC [Internet]. [cited 2018 Oct 17]. Available from: https://www.uicc.org/who-essential-medicines-list

34. Sucena M, Cachapuz I, Lombardia E, Magalhães A, Guimarães JT. Concentração plasmática de lidocaína durante a broncofibroscopia. Rev Port Pneumol. 2004 Jul;10(4):287–96.

35. Cox B, Durieux ME, Marcus M a. E. Toxicity of local anaesthetics. Best Pract Res Clin Anaesthesiol. 2003 Mar;17(1):111–36.

36. gianelly1967.pdf.

37. Wu CL, Liu SS. Intravenous Lidocaine for Ambulatory Anesthesia: Good to Go or Not So Fast?: Anesth Analg. 2009 Dec;109(6):1718–9.

38. Lauretti GR. Mechanisms of analgesia of intravenous lidocaine. Rev Bras Anestesiol. 2008 Jun;58(3):280–6.

39. Intravenous Lidocaine Infusion Facilitates Acute Rehabilitation after Laparoscopic Colectomy. 2007;106(1):8.

40. Frieden J. Antiarrhythmic drugs. Part VII. Lidocaine as an antiarrhythmic agent. Am Heart J. 1965 Nov 1;70(5):713–5.

41. Beckett AH, Boyes RN, Parker JBR. Determination of lignocaine in blood and urine in human subjects undergoing local analgesic procedures. Anaesthesia. 1965 Jul;20(3):294–8.

42. Miller_s_Anesthesia_2-Volume_Set_8E_2015.pdf.

43. Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: A review. World J Anesthesiol. 2015 Jul 27;4(2):17–29.

44. McCann ME, Sethna NF, Mazoit JX, Sakamoto M, Rifai N, Hope T, et al. The pharmacokinetics of epidural ropivacaine in infants and young children. Anesth Analg. 2001 Oct;93(4):893–7.

45. Tucker GT, Mather LE. Pharmacology of local anaesthetic agents. Pharmacokinetics of local anaesthetic agents. Br J Anaesth. 1975 Feb;47 suppl:213–24.

46. Bennett PN, Aarons LJ, Bending MR, Steiner JA, Rowland M. Pharmacokinetics of lidocaine and its deethylated metabolite: dose and time dependency studies in man. J Pharmacokinet Biopharm. 1982 Jun;10(3):265–81.

47. Lidocaine - FDA prescribing information, side effects and uses [Internet]. Drugs.com. [cited 2018 Aug 6]. Available from: https://www.drugs.com/pro/lidocaine.html

48. Collinsworth KA, Kalman SM, Harrison DC. The clinical pharmacology of lidocaine as an antiarrhythymic drug. Circulation. 1974 Dec;50(6):1217–30.

49. Hsu Y-W, Somma J, Newman MF, Mathew JP. Population Pharmacokinetics of Lidocaine Administered During and After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2011 Dec 1;25(6):931–6.

50. Themes UFO. Local Anesthetics [Internet]. Anesthesia Key. 2016 [cited 2018 Oct 17]. Available from: https://aneskey.com/local-anesthetics-5/

51. Wood JN, Boorman JP, Okuse K, Baker MD. Voltage-gated sodium channels and pain pathways. J Neurobiol. 2004 Oct 1;61(1):55–71.

52. Kalso E. Sodium Channel Blockers in Neuropathic Pain [Internet]. Current Pharmaceutical Design. 2005 [cited 2018 Oct 18]. Available from: http://www.eurekaselect.com/60194/article

53. Carver AC, Foley KM. Types of Pain. Holl-Frei Cancer Med 6th Ed [Internet]. 2003 [cited 2018 Oct 18]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK12991/

54. Cervero F. Visceral versus Somatic Pain: Similarities and Differences. Dig Dis. 2009;27(1):3–10.

55. Lidocaine Stock Photos. Royalty Free Lidocaine Images [Internet]. 123RF Stock Photos. [cited 2018 Oct 17]. Available from: https://www.123rf.com/stock-photo/lidocaine.html

56. McCarthy GC, Megalla SA, Habib AS. Impact of Intravenous Lidocaine Infusion on Postoperative Analgesia and Recovery from Surgery: A Systematic Review of Randomized Controlled Trials. Drugs. 2010 Jun;70(9):1149–63.

57. Jendoubi A, Naceur IB, Bouzouita A, Trifa M, Ghedira S, Chebil M, et al. A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: A prospective, double-blind, randomized, placebo-controlled study. Saudi J Anaesth. 2017 Jun;11(2):177–84.

58. Kang JG, Kim MH, Kim EH, Lee SH. Intraoperative intravenous lidocaine reduces hospital length of stay following open gastrectomy for stomach cancer in men. J Clin Anesth. 2012 Sep;24(6):465–70.

59. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011 Apr;14(2):145–61.

60. PROSTAGLANDIN BIOSYNTHESIS IN THE EPIDERMIS AND DERMIS OF YOUNG MOUSE SKIN, AND THE EFFECTS OF CALCIUM AND CYCLIC NUCLEOTIDES - ScienceDirect [Internet]. [cited 2018 Aug 15]. Available from: https://www.sciencedirect.com/science/article/pii/S0022202X15450110

61. Yanagi H, Sankawa H, Saito H, Iikura Y. Effect of lidocaine on histamine release and Ca2+ mobilization from mast cells and basophils. Acta Anaesthesiol Scand. 1996 Oct;40(9):1138–44.

62. Sinclair R, Eriksson AS, Gretzer C, Cassuto J, Thomsen P. Inhibitory effects of amide local anaesthetics on stimulus-induced human leukocyte metabolic

activation, LTB4 release and IL-1 secretion in vitro. Acta Anaesthesiol Scand. 1993 Feb;37(2):159–65.

63. Lahav M, Levite M, Bassani L, Lang A, Fidder H, Tal R, et al. Lidocaine inhibits secretion of IL-8 and IL-1beta and stimulates secretion of IL-1 receptor antagonist by epithelial cells. Clin Exp Immunol. 2002 Feb;127(2):226–33.

64. Modig J. Influence of regional anesthesia, local anesthetics, and sympathicomimetics on the pathophysiology of deep vein thrombosis. Acta Chir Scand Suppl. 1989;550:119–24; discussion 124-127.

65. Toyota S, Moriyama M, Otake T, Kono J, Shudou Y, Satake T, et al. Effect of anaesthetic agents on the phagocytic function of human polymorphonuclear leukocytes through analysis with a phagocytic plaque method. Inflamm Res. 1995 May 1;44(5):204–6.

66. Influence of local anesthetics upon human polymorphonuclear leukocyte function in vitro. Reduction of lysosomal enzyme release and superoxide anion production. J Exp Med. 1977 Aug 1;146(2):483–94.

67. Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine. Anesthesiol J Am Soc Anesthesiol. 2017 Apr 1;126(4):729–37.

68. Hahnenkamp K, Durieux ME, Hahnenkamp A, Schauerte SK, Hoenemann CW, Vegh V, et al. Local anaesthetics inhibit signalling of human NMDA receptors recombinantly expressed in Xenopus laevis oocytes: role of protein kinase C. Br J Anaesth. 2006 Jan;96(1):77–87.

69. Lamacraft G. The link between acute postoperative pain and chronic pain syndromes. South Afr J Anaesth Analg. 2012 Jan;18(1):45–50.

70. Wasiak J, Cleland H. Lidocaine for pain relief in burn injured patients. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005622.

71. de Klaver MJM, Buckingham M-G, Rich GF. Lidocaine attenuates cytokine-induced cell injury in endothelial and vascular smooth muscle cells. Anesth Analg. 2003 Aug;97(2):465–70, table of contents.

72. L CV and L. Mechanism of penetration and of action of local anesthetics in Escherichia coli cells. - PubMed - NCBI [Internet]. [cited 2018 Aug 15]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/2204430

73. Fazly Bazaz BS, Salt WG. Local anaesthetics as antimicrobial agents: structure-action considerations. Microbios. 1983;37(147):45–64.

74. Aydin ON, Eyigor M, Aydin N. Antimicrobial activity of ropivacaine and other local anaesthetics. Eur J Anaesthesiol. 2001 Oct;18(10):687–94.

75. Agarwal N, Kalra VK. Studies on the mechanism of action of local anesthetics on proton translocating ATPase from Mycobacterium phlei. Biochim Biophys Acta. 1984 Mar 30;764(3):316–23.

76. Chiang N, Schwab JM, Fredman G, Kasuga K, Gelman S, Serhan CN. Anesthetics impact the resolution of inflammation. PloS One. 2008 Apr 2;3(4):e1879.

77. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. Acta Anaesthesiol Scand. 2006 Mar;50(3):265–82.

78. Song X, Sun Y, Zhang X, Li T, Yang B. Effect of perioperative intravenous lidocaine infusion on postoperative recovery following laparoscopic Cholecystectomy-A randomized controlled trial. Int J Surg Lond Engl. 2017 Sep;45:8–13.

79. Harvey KP, Adair JD, Isho M, Robinson R. Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. Am J Surg. 2009 Aug;198(2):231–6.

80. Groeben H, Schwalen A, Irsfeld S, Stieglitz S, Lipfert P, Hopf H-B. Intravenous Lidocaine and Bupivacaine Dose-dependently Attenuate Bronchial Hyperreactivity in Awake Volunteers. Anesthesiol J Am Soc Anesthesiol. 1996 Mar 1;84(3):533–9.

81. Brown RH, Robbins W, Staats P, Hirshman C. Prevention of bronchoconstriction by an orally active local anesthetic. Am J Respir Crit Care Med. 1995 Apr;151(4):1239–43.

82. Intravenous lidocaine and oral mexiletine block reflex bronchoconstriction in asthmatic subjects. | American Journal of Respiratory and Critical Care Medicine [Internet]. [cited 2018 Aug 16]. Available from: https://www.atsjournals.org/doi/abs/10.1164/ajrccm.154.4.8887580?related-urls=yes&ck=nck&legid=ajrccm%3B154%2F4%2F885

83. Kaneishi K, Kawabata M. Continuous subcutaneous infusion of lidocaine for persistent hiccup in advanced cancer. Palliat Med. 2013 Mar;27(3):284–5.

84. Neeno TA, Rosenow EC. Intractable Hiccups-To the Editor: Consider Nebulized Lidocaine. Chest. 1996 Oct 1;110(4):1129–30.

85. Cohen SP, Lubin E, Stojanovic M. Intravenous lidocaine in the treatment of hiccup. South Med J. 2001 Nov;94(11):1124–5.

86. Dunst MN, Margolin K, Horak D. Lidocaine for Severe Hiccups [Internet]. 2010 [cited 2018 Aug 17]. Available from: https://www.nejm.org/doi/10.1056/NEJM199309163291222?url_ver=Z39.88-

2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov

87. Boulouffe C, Vanpee D. Severe hiccups and intravenous lidocaine. Acta Clin Belg. 2007 Apr;62(2):123–5.

88. Couceiro et al. - 2014 - Intravenous lidocaine to treat postoperative pain.pdf.

89. Joshi GP, Bonnet F, Kehlet H, PROSPECT collaboration. Evidence-based postoperative pain management after laparoscopic colorectal surgery. Colorectal Dis Off J Assoc Coloproctology G B Irel. 2013 Feb;15(2):146–55.

90. Kindler CH, Yost CS. Two-pore domain potassium channels: new sites of local anesthetic action and toxicity. Reg Anesth Pain Med. 2005 Jun;30(3):260–74.

91. Lui KC, Chow YF. Safe use of local anaesthetics: prevention and management of systemic toxicity. Hong Kong Med J Xianggang Yi Xue Za Zhi. 2010 Dec;16(6):470–5.

92. DeToledo JC. Lidocaine and seizures. Ther Drug Monit. 2000 Jun;22(3):320–2.

93. 2005-Daquan-Porcine-Phantom.pdf [Internet]. [cited 2018 Aug 19]. Available from: https://www.ultrasoundtraining.com.au/sb_cache/news/id/372/f/2005-Daquan-Porcine-Phantom.pdf

94. Franco A, Diz JC. The history of the epidural block. Curr Anaesth Crit Care. 2000 Oct 1;11(5):274–6.

95. Royse C, Royse A, Soeding P, Blake D, Pang J. Prospective randomized trial of high thoracic epidural analgesia for coronary artery bypass surgery. Ann Thorac Surg. 2003 Jan;75(1):93–100.

96. Pöpping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. Br J Anaesth. 2008 Dec;101(6):832–40.

97. Clemente A, Carli F. The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems. Minerva Anestesiol. 2008 Oct;74(10):549–63.

98. Meissner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks, and controversies. Anesth Analg. 1997 Sep;85(3):517–28.

99. Freise H, Aken V, K H. Risks and benefits of thoracic epidural anaesthesia. BJA Br J Anaesth. 2011 Dec 1;107(6):859–68.

100. Tenenbein PK, Debrouwere R, Maguire D, Duke PC, Muirhead B, Enns J, et al. Thoracic epidural analgesia improves pulmonary function in patients undergoing cardiac surgery. Can J Anesth. 2008 Jun 1;55(6):344–50.

101. Svircevic V, van Dijk D, Nierich AP, Passier MP, Kalkman CJ, van der Heijden GJMG, et al. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. Anesthesiology. 2011 Feb;114(2):271–82.

102. Sielenkämper AW, Eicker K, Van Aken H. Thoracic epidural anesthesia increases mucosal perfusion in ileum of rats. Anesthesiology. 2000 Sep;93(3):844–51.

103. Hiltebrand LB, Koepfli E, Kimberger O, Sigurdsson GH, Brandt S. Hypotension during fluid-restricted abdominal surgery: effects of norepinephrine treatment on regional and microcirculatory blood flow in the intestinal tract. Anesthesiology. 2011 Mar;114(3):557–64.

104. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev. 2000;(4):CD001893.

105. Nishimori M, Ballantyne JC, Low JHS. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD005059.

106. Tyagi A, Seelan S, Sethi AK, Mohta M. Role of thoracic epidural block in improving post-operative outcome for septic patients: a preliminary report. Eur J Anaesthesiol. 2011 Apr;28(4):291–7.

107. Michelet P, D'Journo X-B, Roch A, Papazian L, Ragni J, Thomas P, et al. Perioperative risk factors for anastomotic leakage after esophagectomy: influence of thoracic epidural analgesia. Chest. 2005 Nov;128(5):3461–6.

108. Zügel N, Bruer C, Breitschaft K, Angster R. [Effect of thoracic epidural analgesia on the early postoperative phase after interventions on the gastrointestinal tract]. Chir Z Alle Geb Oper Medizen. 2002 Mar;73(3):262–8.

109. Holte K, Kehlet H. Epidural analgesia and risk of anastomotic leakage. Reg Anesth Pain Med. 2001 Apr;26(2):111–7.

110. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. Oncotarget. 2016 Feb 24;7(12):15262–73.

111. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law P-Y, Yee D, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-

promoting signaling and promotes breast tumor growth. Cancer Res. 2002 Aug 1;62(15):4491–8.

112. Yeager MP, Colacchio TA. Effect of morphine on growth of metastatic colon cancer in vivo. Arch Surg Chic Ill 1960. 1991 Apr;126(4):454–6.

113. Farooqui M, Li Y, Rogers T, Poonawala T, Griffin RJ, Song CW, et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer. 2007 Dec 3;97(11):1523–31.

114. Yeager MP, Colacchio TA, Yu CT, Hildebrandt L, Howell AL, Weiss J, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology. 1995 Sep;83(3):500–8.

115. Safety and Patient-Controlled Analgesia Part 2: How to Prevent Errors. :2.

116. Kleif J, Waage J, Christensen KB, Gögenur I. Systematic review of the QoR-15 score, a patient- reported outcome measure measuring quality of recovery after surgery and anaesthesia. Br J Anaesth. 2018 Jan 1;120(1):28–36.

117. Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. Br J Anaesth. 2000 Jan;84(1):11–5.

118. Stark PA, Myles PS, Burke JA. Development and Psychometric Evaluation of a Postoperative Quality of Recovery Score: The QoR-15. Anesthesiology. 2013 Jun;118(6):1332–40.

119. Colorectal Cancer - Cancer Stat Facts [Internet]. [cited 2018 Sep 24]. Available from: https://seer.cancer.gov/statfacts/html/colorect.html

120. Staikou C, Avramidou A, Ayiomamitis GD, Vrakas S, Argyra E. Effects of Intravenous Versus Epidural Lidocaine Infusion on Pain Intensity and Bowel Function After Major Large Bowel Surgery: a Double-Blind Randomized Controlled Trial. J Gastrointest Surg. 2014 Dec 1;18(12):2155–62.

121. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. BJA Educ. 2016 Sep;16(9):292–8.

122. Haughton VM, Fine J. Measuring the Effect of Novel Therapies for Back Pain. Am J Neuroradiol. 2003 May 1;24(5):784–7.

123. Katz J, Melzack R. MEASUREMENT OF PAIN. Surg Clin North Am. 1999 Apr 1;79(2):231–52.

124. Khan JS, Yousuf M, Victor JC, Sharma A, Siddiqui N. An estimation for an appropriate end time for an intraoperative intravenous lidocaine infusion in bowel surgery: a comparative meta-analysis. J Clin Anesth. 2016 Feb;28:95–104.

ANNEXURES

ANNEXURE – 1 – IRB APPROVAL

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 Re Reg-2016 Issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, M.B.B.S., D. Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. L. Jeyaseelan, M.Sc., Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., MA (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Ref: IRB – A11 - 22.11.2017

December 09, 2017

Dr. Namitha B J,
Department of Anaesthesia,
Christian Medical College,
Vellore 632 002

Ref: IRB Min No.10542 dated 20.03.2017

Dear Dr. Namitha B J,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed the following amendment for the study titled "Continuous intravenous 2% liocaine infusion or thoracic epidural analgesia for postoperative pain in laparoscopic anterior resection: A comparison" on November 22nd 2017.

1. To include patients undergoing laparoscopic sigmoid colectomy for anorectal cancer in our study group as the operative differences between the two surgeries are minimal and does not affect the outcome of our study

The following Institutional Review Board (Silver, Research & Ethics Committee) members were present at the meeting held on November 22nd 2017 at 9.45 am in the New Examination Hall, 2nd Floor Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. George Thomas	MBBS, D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB, Chennai	External, Clinician
Dr. L. Jeyaseelan	MSc, PhD, FSMS, FRSS	Professor, Biostatistics, Secretary (Research Committee), IRB, CMC, Vellore	Internal, Statistician
Rev. Dr. T. Arul Dhas	MSc, BD, DPC, PhD(Edin)	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. Shirley David	MSc, PhD	Professor, Head of Fundamentals Nursing Department, College of Nursing, CMC, Vellore	Internal, Nurse

Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Additional Vice Principal (Research), Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore.	Internal, Clinician
Dr. Prasanna Samuel	MSc, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External, Clinician
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP, FRCPCH	Professor of Paediatrics, Community Medicine, CMC, Vellore	Internal, Clinician
Dr. D. J. Christopher	BSc, MBBS, DTCD DNB, FRCP(Glasg), FCCP(USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Ashish Goel	MBBS, MD, DM	Professor, Hepatology, CMC, Vellore	Internal, Clinician
Dr. RV Shaji	BSc, MSc, PhD	Professor, Heamatology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Sridhar Gibikote	MBBS, DMRD, DNB	Professor, Radiology, CMC, Vellore	Internal, Clinician
Dr. Sujith J Chandy	MBBS., MD., PhD., FRCP (E)	Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert

Mrs. Ruma Nayak	M Sc (Nursing)	Professor, Head of Paediatric Nursing & Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio-Engineering, CMC, Vellore	Internal,Basic Medical Scientist
Dr. Jacob John	MBBS, MD, MPH	Professor, Community Medicine, CMC, Vellore	Internal, Clinician
Dr. Vinitha Ravindran	PhD (Nursing)	Professor & Addl. Deputy Dean, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio-Engineering, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Sathya Subramani	MD, PhD	Professor, Physiology, CMC, Vellore	Internal, Clinician
Dr. Jiji Elizabeth Mathews	MBBS, DGO, MD,	Professor, Obstetrics & Gynaecology, CMC, Vellore	Internal, Clinician
Dr. Abhay Gahukamble	MS, D Ortho, DNB(Ortho)	Associate Professor, Paediatric Orthopaedics, CMC, Vellore	Internal, Clinician

We approve the above amendment as presented.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board.

Dr. BIJU GEORGE
SECRETARY - ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

ANNEXURE – 2 – CONSENT FORM

Consent to take part in a Clinical Trial

STUDY TITLE:

Continuous Intravenous 2% Lidocaine infusion or Thoracic Epidural Analgesia for postoperative pain in Laparoscopic Anterior Resection: A Comparison.

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____

_____, son/daughter/wife of _____

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I understand that I will receive free treatment for any study related injury or adverse event but I will not receive any other financial compensation [ ]

I understand that the Study staff , the Institutional Ethics Committee and the Regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

STUDY TITLE:

Continuous Intravenous 2% Lidocaine infusion or Thoracic Epidural Analgesia for postoperative pain in Laparoscopic Anterior Resection: A Comparison

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I agree to pay for any investigation routinely warranted for my treatment [ ]

I voluntarily agree to take part in this study [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature: _____

Or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

CONSENT FORM – BENGALI

একটি ক্লিনিকাল ট্রায়াল এ অংশগ্রহণ করার অনুমতি পত্র

পরীক্ষার বিষয়:

পরীক্ষার সংখ্যা:

অংশগ্রহণকারীর নাম:

জন্মতারিখ (বয়স)(বছর এ):

আমি _____ _____
এর স্ত্রী/ স্বামী/ পুত্র/ কন্যা

(টিক দিন)

বলছি যে রোগীর তথ্যপত্রটি পড়েছি এবং যা সন্দেহ ছিল সব পুরস্কার করে জিগেশ করে নিয়েছি [ ]

এটাও বলছি যে এই পরীক্ষায় অংশগ্রহণ করা সম্পূর্ণ আমার স্বেচ্ছায় এবং আমি যেকোনো সময় এই পরীক্ষা থেকে সরে আসতে পারি আমার স্বাভাবিক চিকিৎসায়, আইনত অধিকারে তার কোনো প্রভাব পর্বে না [ ]

আমি বুঝলাম চিকিৎসার জন্যে কোনো ক্ষতির ক্ষেত্রে আর্থিক মূল্য পাবো না কিন্তু সমস্যা কিছু হলে বিনামূল্য চিকিৎসা পাবো [ ]

আমি বুঝলাম যে এথিক্স কমিটির পক্ষ থেকে কেউ অথবা তদন্তকারী আমার পরীক্ষার তথ্য নিতে চাইলে আমি তা দিতে রাজি আছি, এমন কি আমি এই গবেষণা থেকে সরে দাড়ালেও। এটি বর্তমান গবেষণা এমং ভবিষৎ অনুরুপ গবেষনার জন্যও প্রযোজ্য। তবে আমার পরিচয় যেকোনো ক্ষেত্রেই গোপন থাকবে। [ ]

এই গবেষণায় যেকোনো তথ্য আমি বৈজ্ঞানিক কাজের জন্যেই ব্যবহার করতে দিতে সম্মত আছি। [ ]

আমার পরিচয় কোনো তৃতীয় ব্যাক্তির কাছে বা বৈজ্ঞানিক কোন পত্রিকায় প্রকাশিত হবে না [ ]

নিয়মিত পরীক্ষার জন্যে খরচ আমি নিজেই দেব [ ]

আমি স্বেচ্ছায় এই পরীক্ষায় অংশগ্রহণ করছি [ ]

স্বাক্ষর (বা আঙ্গুল ছাপ) অংশগ্রহনকারীর (আইনত গ্রহণযোগ্য)

তারিখ: _____ / _____ / _____

স্বাক্ষরকারী এর নাম: _____ স্বাক্ষর:

বা

প্রতিনিধি: _____

প্রতিনিধি: _____

তারিখ: _____ / _____ / _____

স্বাক্ষরকারী এর নাম: _____

তদন্তকারীর স্বাক্ষর: _____

তারিখ: _____ / _____ / _____

গবেষণায় তদন্তকারী এর নাম: _____

সাক্ষীর স্বাক্ষর বা টিপসই: _____

তারিখ: _____ / _____ / _____

নাম ও সাক্ষী ঠিকানা: _____

CONSENT FORM - HINDI

सहमति के एक क्लीनिकल ट्रायल में भाग लेने के लिए

अध्ययन शीर्षक:

सतत नर्सों में 2% lidocaine अर्क या लेप्रोस्कोपिक पूर्वकाल लकीर में पश्चात दर्द के लिए छाती रोगों एपीड्यूरल Analgesia: एक तुलना।

अध्ययन संख्या:
प्रतिभागी का नाम:
जन्म / आयु (वर्षों में) की तारीख:

मैं_____
_____, बेटा / बेटी / पत्नी के _____

(कृपया बक्से टिकटिक)
डिक्लेयर करता हूं कि मैंने इस अध्ययन के बारे में मुझे प्रदान किया गया सूचना पत्र पढ़ लिया है और मेरे हर संदेह को स्पष्ट किया गया है। [ ]
मैं यह भी समझतो हु कि इस अध्ययन में मेरी भागीदारी पूरी तरह स्वैच्छिक है और मैं अपने सामान्य उपचार या मेरे कानूनी अधिकार प्रभावित किए बिना किसी भी समय भाग लेने के लिए जारी रखने के लिए अनुमति वापस लेने के लिए स्वतंत्र हूँ.
मैं समझता हूँ कि मुझे किसी भी अध्ययन से संबंधित चोट या प्रतिकूल घटना के लिए नि: शुल्क उपचार प्राप्त होगा, लेकिन मुझे किसी भी अन्य वित्तीय क्षतिपूर्ति प्राप्त नहीं होगी [ ]
मैं समझता हूँ कि अध्ययन कर्मचारियों, संस्थागत आचार समिति और नियामक अधिकारियों को दोनों वर्तमान अध्ययन और किसी भी आगे अनुसंधान के संबंध में मेरे स्वास्थ्य के रिकॉर्ड को देखने के लिए मेरी अनुमति की जरूरत नहीं होगी, भले ही मैं परीक्षण से निकल जाऊँ। मैं इस का उपयोग करने के लिए सहमती देता हु। हालांकि, मैं समझता हूँ कि मेरी पहचान तीसरे पक्ष के लिए जारी या प्रकाशित किसी भी जानकारी में पता नहीं कि जाऐगी। []
मैं अध्ययन से उत्पन्न होनेवाले किसी भी डेटा या परिणाम कि केवल वैज्ञानिक उद्देश्य (ओं) के लिए उपयोग करने कि सहमती देता(ती) हु। [ ]

मैं समझता हूँ कि मेरी पहचान का किसी भी जानकारी में खुलासा नहीं किया जाएगा[ ]
मैं नियमित रूप से मेरे इलाज के लिए झरुरी किसी भी जांच के लिए भुगतान करने के लिए सहमत हु[ ]
मैं स्वेच्छा से इस अध्ययन में भाग लेने के लिए सहमती देता(ती) हु। [ ]

हस्ताक्षर (या अंगूठे का निशान) विषय की / कानूनी तौर पर स्वीकार्य

तारीख: _____/_____/_____

हस्ताक्षरकर्ता का नाम: _____ हस्ताक्षर: _____

या

प्रतिनिधि: _____

तारीख: _____/_____/_____

हस्ताक्षरकर्ता का नाम: _____

अन्वेषक के हस्ताक्षर: _____

तारीख: _____/_____/_____

अध्ययन जांचकर्ता का नाम: _____

गवाह का हस्ताक्षर या अंगूठे का निशान: _____

तारीख: _____/_____/_____

नाम व गवाह का पता: _____

ANNEXURE – 3 – PATIENT INFORMATION SHEET

Christian Medical College, Vellore

Department of Anaesthesia

TITLE: Continuous intravenous 2% Lidocaine infusion or Thoracic Epidural Analgesia for postoperative pain in laparoscopic Anterior Resection and sigmoid colectomy : A comparison.

You are invited to be part of a study to improve the current knowledge regarding various methods of pain relief and overall quality of recovery after laparoscopic abdominal surgery. Please take time to read / listen to the following information.

DESCRIPTION OF THE STUDY

The information collected from you will include -

1. History – This includes details regarding your general health and the disease for which you are undergoing the surgery.
2. Clinical examination – Besides the regular doctors rounds, the primary investigator will examine you regularly.

You will be seen in the ward by the anaesthetist after your surgery and information will be collected using a questionnaire of 15 questions. You are scheduled to undergo keyhole abdominal operation under general anaesthesia. Pain after this surgery is one of the major causes of patient discomfort and prolonged duration of hospital stay. It also affects the overall quality of recovery.

There are various methods to control such pain after surgery, of which Epidural catheter insertion and Intravenous Lidocaine are two of the most effective.

Epidural analgesia involves inserting a needle at the back before the surgery in the operation theatre by the anaesthetist. A small catheter will be introduced around the layers of spinal cord through which pain relief medication will be continuously provided through a pump for the next 48 hours.

The second method involves giving a medicine called Lidocaine (a local anaesthetic) through the veins continuously for the entire duration of surgery.

Both these methods are known to be good options for pain control. However, we still do not have enough research to come to a conclusion on which is better for keyhole surgeries. Hence we would like to compare these two modes.

On consenting to be a part of this study you will be randomly allotted into one of two groups.

These methods are well studied and are found to be effective and safe to use with minimal side effects. The operative technique and all other anaesthetic approaches will be the same in both groups.

If you experience pain at any time after surgery, you will be treated with an additional dose of pain killer.

FORSEEABLE RISKS OR INCONVENIENCES: There may be on rare occasions, the following effects. When any of the following events occur, you are to report to the doctor/nursing staff immediately and treatment for the same will be given free of cost.

1) Dizziness

2) Confusion

3) Tingling and numbness around the mouth

4) Metallic taste in the mouth

5) Seizures

6) Ringing in the ears

7) Slowing of heart rate

8) Fall in BP

All details including personal data, assessment of the doctor during and after the operation will be kept confidential. Your decision regarding participation in this study will not affect your further treatment at this hospital. Although you may or may not directly benefit by enrolling in the study, you will be contributing to scientific knowledge. There will be no monetary benefit provided.

Participation in this study is purely voluntary, and you can withdraw from the study at any time. Your refusal to participate will not affect your treatment in the hospital.

INFORMATION SHEET – BENGALI

বৈজ্ঞানিক গবেষনার জন্যে রোগীকে অবগত করার তথ্য সমূহ:

গ্রীষ্টান মেডিকেল কলজ ভেলোর

অজ্ঞান করার বিভাগ :

২% লিগ্নোকেইনে দিয়ে নিরবিচ্ছিন্ন ব্যাথা কমানোর সাথে থোরাসিক এপিডুরাল ব্যাথা কমানোর পদ্ধতির তুলনা, ল্যাপারোস্কপি করে পিটার অস্ত্রপ্রচারের ক্ষেত্রে

ল্যাপারোস্কপি করে পেটের অস্ত্রপ্রচারের ক্ষেত্রে ব্যাথা কমানোর বিভিন্ন পদ্ধতির মধ্যে কোনটি বেশি ভালো জানার একটা পরীক্ষা করা হচ্ছে । এটিতে আপনাকে যোগদান করতে আওহ্বান করা হচ্ছে ।এই পরীক্ষা করে বাকি রুগীদের যারা একই অপারেশান করছেন তাদের উপকার হবে ।এই পরীক্ষায় অংশগ্রহণ করে আপনি বিজ্ঞানের উন্নতি করবেন । এই ব্যাপারে কোনো প্রশ্ন থাকলে আপনি জিগেস করতে পারেন ।

এই পরীক্ষার পদ্ধতি:

এই পরীক্ষায় আপনার রজার ইতিহাস নেওয়া হবে এবং রোজ চেক আপ চলতে থাকবে । আপনার প্রাথমিক ডাক্তার ছাড়া এই পরীক্ষার ডাক্তার আপনাকে নিয়মিত পরীক্ষা করবেন ।

অপারেশনের পরে আপনাকে এই পরীক্ষার ডাক্তার পনেরোটি প্রশ্ন করে আপনার থেকে কিছু তথ্য নেবেন । আপনি এই পরীক্ষায় অংশগ্রহণ করবেন কিনা সেটা আপনার এখানে চিকিৎসায় কোনো প্রভাব ফেলবে না । আপনি সোজাসুজি কোনো উপকারিতা যদি নাও পান তাহলেও আমাদের গবেষণা সফল হলে ভবিষ্যত প্রজন্ম উপকৃত হবে । এর জন্যে আপনি কোনো টাকা পাবেন না ।

আপনি পেটের অস্ত্রপ্রচারের জন্যে ভর্তি হয়েছেন যেটা অস্ত্রপ্রচারের পরে অনেকটা ব্যাথা করতে পারে এবং অনেকদিন হাসপাতালে থাকতে হতে পারে ।

এই ব্যাথা কমানোর অনেক পদ্ধতি আছে যেগুলোর মধ্যে দুটো আমরা ব্যবহার করে থাকি ।

একটিতে আপনার সুষুম্নাকান্ডের মধ্যে ৪৮ ঘন্টা পর্যন্ত ব্যাথার ওষুধ অল্প অল্প করে দেওয়া হবে ।

এর জন্যে অজ্ঞান করার ডাক্তার আপনার পিঠে একটি ছোট ছিদ্র করে সরু একটা টিউব পুড়ে দেবেন সেটা দিয়ে ওষুধ যাবে ।

আর আরেকটা পদ্ধতিতে লিগ্নোকেন আপনাকে অল্প অল্প করে ড্রিপ এর মাদ্ধমে দেওয়া হবে । এই পরীক্ষায় যোগদান করলে আপনি এই দুটির মধ্যে যেকোনো একটি দোলে পড়বেন ।

দুটো পদ্ধতি ই বিজ্ঞান সম্মত এবং নিরাপদ ।

অপারেশন করার পদ্ধতিতে কোনো পার্থক্য থাকবে না ।

যদি কোনো বেশি ব্যাথা করে তাহলে আমরা ফেনটানিল বলে আরেকটা ওষুধ দেব ।

বিপদের সম্ভবনা :

i. অর কিছু ক্ষেত্রে যদি নিচের গুলি হয় তাহলে অবশ আমাদের জানাবেন---
ii. মাথা ঘোরা
iii. অসংলগ্ন চিন্তা করা
iv. মুখের চারপাশে অবশ হয়ে যাওয়া
v. মুখের মধ্যে ধাতব স্বাদ
vi. খিঁচুনি
vii. কানে ভোঁ ভোঁ শব্দ
viii. হৃদস্পন্দন কমে যাওয়া
ix. রক্তচাপ কমে যাওয়া মনে হওয়া

আপনার থেকে পাওয়া সব তথ্য গোপন রাখা হবে । আমরা পঞ্চাশ জন রুগী কে দুবছরে এই পরীক্ষায় যোগদান করতে চাই । এই পরীক্ষায় যোগদান করা একেবারেই স্বেচ্ছায় এবং কখন কারণে আপনি যদি ইটা ছেড়ে যেতে চান তাতে কোনোরকম ক্ষতিপূরণ আপনাকে দিতে হবে না ।

INFORMATION SHEET – HINDI

सूचना पत्र
क्रिश्चियन मेडिकल कॉलेज, वेल्लोर
एनेस्थीसिया विभाग

शीर्षक: सतत नसों में 2% lidocaine अर्क या लेप्रोस्कोपिक पूर्वकाल लकीर में पश्चात दर्द के लिए छाती रोगों एपीड्यूरल Analgesia: एक तुलना।

आपको लेप्रोस्कोपिक पेट की सर्जरी के बाद दर्द से राहत और रीकवरी के समग्र गुणवत्ता के विभिन्न तरीकों के बारे में वर्तमान ज्ञान में सुधार करने के लिए एक अध्ययन का हिस्सा बनने के लिए आमंत्रित किया गया हैं। कृपया / पढ़ने के लिए निम्नलिखित जानकारी को सुनने के लिए समय ले लो। अध्ययन कर्मि किसी भी प्रश्न / स्पष्टीकरण का जवाब देने के लिए उपलब्ध है।

अध्ययन का विवरण

जानकारी जो आप से ली जाऐगी-
इतिहास - यह अपने सामान्य स्वास्थ्य और बीमारी है जिसके लिए आप सर्जरी के दौर से गुजर रहे हैं के बारे में जानकारी शामिल है।
नैदानिक परीक्षा - इसके अलावा नियमित रूप से डॉक्टरों दौर, प्राथमिक अन्वेषक आप नियमित रूप से जांच करेंगे।

आप वार्ड में एनेस्थेटिस्ट द्वारा जांच की जाएगी अपनी सर्जरी और जानकारी 15 सवालों की एक प्रश्नावली का उपयोग कर एकत्र किया जाएगा।
आप सामान्य संज्ञाहरण के तहत लेप्रोस्कोपिक पूर्वकाल लकीर गुजरना करने के लिए निर्धारित कर रहे हैं। सर्जरी के बाद दर्द के रोगी असंतोष और लंबे समय तक अस्पताल में रहने के प्रमुख कारणों में से एक है। यह भी वसूली की समग्र गुणवत्ता को प्रभावित करता है।
वहाँ वसूली के दौरान इस तरह के दर्द, जिनमें से एपीड्यूरल Analgesia और नसों में Lidocaine सबसे प्रभावी में से दो हैं नियंत्रित करने के विभिन्न तरीके हैं।
एपीड्यूरल analgesia एनेस्थेटिस्ट द्वारा आपरेशन थियेटर में सर्जरी से पहले पीठ पर एक सुई डालने शामिल है। एक छोटा सा कैथेटर रीढ़ की हड्डी की परतों के माध्यम से जो दर्द निवारक दवा लगातार अगले 48 घंटे के लिए एक पंप के माध्यम से उपलब्ध कराया जाएगा आसपास पेश किया जाएगा।
दूसरी विधि सर्जरी की पूरी अवधि के लिए लगातार नसों के माध्यम से एक दवा Lidocaine कहा जाता है (एक स्थानीय संवेदनाहारी) दे रही शामिल है।
इन दोनों तरीकों दर्द नियंत्रण के लिए अच्छा विकल्प हो जाना जाता है। हालांकि, हम अभी भी एक निष्कर्ष है जिस पर लेप्रोस्कोपिक सर्जरी के लिए बेहतर है के लिए आने के लिए पर्याप्त अनुसंधान की जरूरत नहीं है। इसलिए हम इन दोनों साधनों के बीच तुलना करना चाहते हैं।
इस अध्ययन आप बेतरतीब ढंग से दो समूहों में से एक में आवंटित किया जाएगा का एक हिस्सा होने के लिए सहमति दे पर। रोगियों के एक समूह को 48 घंटे, दर्द की दवा (Bupivacaine) की निरंतर वितरण है जिसके माध्यम से, जबकि दूसरे समूह में रोगियों को सर्जरी के दौरान नसों Lidocaine प्राप्त होगा के लिए एक एपीड्यूरल कैथेटर होगा।
इन तरीकों में अच्छी तरह से अध्ययन कर रहे हैं और प्रभावी और कम से कम साइड इफेक्ट के साथ प्रयोग करने के लिए सुरक्षित होना पाया जाता है। ऑपरेटिव तकनीक और अन्य सभी संवेदनाहारी के दृष्टिकोण समान हो जाएगा।
आप सर्जरी के बाद किसी भी समय दर्द का अनुभव करते हैं, तो आप दर्द हत्यारा अर्थात Fentanyl

बचाव के लिए दवा के रूप में (एक डिवाइस पीसीए पंप के रूप में जाना जाता है का उपयोग) के एक अतिरिक्त खुराक के साथ इलाज किया जाएगा।

निकट जोखिम या असुविधाओं:

वहाँ, निम्न प्रभाव दुर्लभ अवसरों पर हो सकता है। जब निम्नलिखित घटनाओं से कोई भी हो, तो आप तुरंत चिकित्सक / नर्सिंग स्टाफ को रिपोर्ट करने के लिए कर रहे हैं।

1) चक्कर आना
2) भ्रम
3) झुनझुनी और मुंह के आसपास अकड़ना
4) मुँह में धातु स्वाद
5) बरामदगी
6) कान में बज रहा
7) दिल की दर के धीमा
8) बी.पी. में गिर

के दौरान और ऑपरेशन के बाद व्यक्तिगत डेटा, डॉक्टर के मूल्यांकन सहित सभी विवरण गोपनीय रखा जाएगा। इस अध्ययन में अपने निर्णय के बारे में भागीदारी के इस अस्पताल में अपने आगे के उपचार को प्रभावित नहीं करेगा। यद्यपि आप का सीधे अध्ययन में दाखिला द्वारा नहीं लाभ हो सकता है /हो सकता है, आपका वैज्ञानिक ज्ञान के लिए योगदान होगा। वहाँ कोई मौद्रिक लाभ नहीं होगा।

इस अध्ययन में भागीदारी पूरी तरह स्वैच्छिक है, और आप किसी भी समय इस अध्ययन से वापस ले सकते हैं। भाग लेने के लिए कोई जुर्माना या लाभ के नुकसान को शामिल नहीं होगा ।

संदेह / सवाल के मामले में, कृपया संपर्क करें:

डॉ नमिथा बी जे,
एनेस्थीसिया विभाग,
सि. ऐम. सि. ऐ. च. वेल्लोर।

ANNEXURE – 4 – PROTOCOL SHEET

A. Inclusion Criteria:

- All patients undergoing laparoscopic Anterior Resection/ Low Anterior Resections/ Ultra Low Anterior Resection / Sigmoid Colectomy for either cancerous / non cancerous lesions.
- Age > 18 yrs
- ASA 1 & 2

B. Exclusion Criteria:

- ASA 3 & 4
- Electrolyte disturbances
- Allergy to local anaesthetic
- Seizure disorder
- Anti-arrhythmic drug intake within 1 week before surgery
- Psychiatric disorders
- Steroid treatment
- Chronic opioid treatments
- Conversion to laparotomy

Preoperative steps:

1. Informed consent obtained.
2. Preoperative QoR 15 score assessed on the day before the surgery.

Steps in operating theatre:

1. In the operating room intravenous access is obtained and standard monitoring with E.C.G, pulse oximetry, and noninvasive blood pressure monitoring used as indicated for the case.
2. The patients are randomly allocated into two groups using a computer generated block randomization . **Group A** will receive intravenous 2% Lidocaine and **Group B** will have Thoracic Epidural Analgesia (TEA).
3. Patients in Group A will receive 2 mg/Kg weight of 2% lidocaine prior to induction of anaesthesia and followed by an infusion of 2mg/kg/hour of 2% Lidocaine till 30 minutes after surgery.
4. Patients in Group B will have placed, under strict aseptic conditions, a thoracic epidural catheter between the eight and nine or nine and ten thoracic vertebrae prior to induction of anaesthesia. A 3--5 ml bolus of 0.25% Bupivacaine will be administered and infusion at 5 – 8 ml/h.
5. Epidural infusion will be continued after the end of surgery with a premixed syringe containing 0.1 % Bupivacaine and 2mcg/cc Fentanyl till 48 hours after surgery.
6. Systolic, diastolic, mean blood pressure and heart rate, saturation to be recorded at baseline, post intubation and post extubation in the recovery.
7. Intraoperative total analgesic (fentanyl, paracetamol, tramadol, NSAIDS) used will be noted in the data sheet.

8. After extubation, another 22G/24G intravenous access is obtained for the CADD pump which will deliver a bolus of intravenous fentanyl 20 mcg with a lockout period of 15 minutes and no background infusion.
9. Haemodynamic parameters will be recorded in the recovery room every 30 minutes till patient is discharged to the ward.

ANNEXURE – 5 – DATA SHEET

DATA SHEET

Name:					Hosp. No:			
Perioperative Details:								
Age:		**Gender:**	**Male**	**Female**	**ASA**	**1**	**2**	**3**
Weight		**Height**		**BMI**				

Comorbidities - HYPERTENSION / DIABETES MELLITUS/
BRONCHIAL ASTHMA / THYROID DISEASE/

INTRAOPERATIVE DETAILS:

DRUGS	TOTAL DOSE	FLUIDS	TOTAL
Fentanyl		Crystalloid	
Morphine		Colloid	
Paracetamol		Blood	
Nsaids			
Tramadol			

Intraoperative blood loss (ml)	
Total fluids (ml)	
Intraoperative Durations HH:MM	
Surgery	
Anaesthesia	
Lidocaine infusion	
Thoracic Epidural infusion	

POST ANAESTHESIA CARE UNIT DETAILS (RECOVERY ROOM):

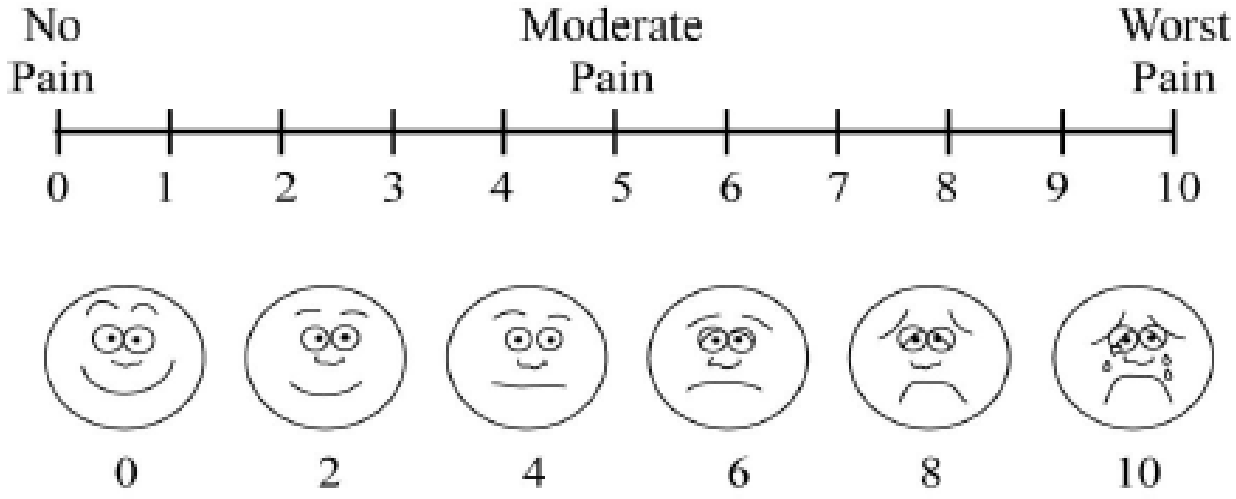
	Baseline (pre-induction)	5min (arrival)	30 min	1hr	1.5 hr	2 hr
Pulse						
SBP						
DBP						
MAP						
Spo2(%)						
RR						
Pain score						
Analgesic drug given: Time(min) Dose(mg)						

Lidocaine related side effects:		
Numbness, tingling in limbs	Y	N
Dizziness	Y	N
Tinnitus	Y	N
Confusion	Y	N
Nausea , vomiting	Y	N
Tremors	Y	N
Convulsions	Y	N
Cardiac arrhythmias/arrest	Y	N

Thoracic Epidural Analgesia related side effects:		
Hypotension	Y	N
Urinary retention	Y	N
Catheter misplacement	Y	N
Unilateral Effect	Y	N
Level of analgesia		
Motor power		

POST OPERATIVE WARD:

Time	Arrival	2hr	4hr	8hr	12hr	24hr
Pain score						
No. Of fentanyl pulses (CADD PUMP)						



Time of discharge from Hospital (post op day): _____

(Time is calculated from the time of end of surgery)

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time

QoR 15 PREOPERATIVE SCORE:_____

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time

QoR 15 POST-OPERATIVE SCORE: 24HRS - 48HRS:_____

ANNEXURE – 6 - CTRI

Clinical Trial Details (PDF Generation Date :- Sat, 20 Oct 2018 14:27:35 GMT)

CTRI Number	CTRI/2018/02/011751 [Registered on: 07/02/2018] - **Trial Registered Retrospectively**
Last Modified On	24/02/2018
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Drug Surgical/Anesthesia
Study Design	Randomized, Parallel Group Trial
Public Title of Study	A study to compare two different modes of pain relief techniques (continuous delivery of Lidocaine (a pain killer) through the vein and epidural infusion(delivery of pain killer around the layers of spinal cord) in all patients undergoing keyhole surgery for colon cancer
Scientific Title of Study	Continuous Intravenous Lidocaine infusion or Thoracic Epidural Analgesia for postoperative pain in Laparoscopic Anterior Resection and sigmoid colectomy: A Comparison.

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Namitha B J
Designation	PG Resident
Affiliation	Christian Medical College
Address	Department of Anaesthesiology, Christian Medical College,Vellore Vellore TAMIL NADU 632004 India
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Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
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Details Contact Person (Public Query)

Details Contact Person (Public Query)	
Name	Namitha B J
Designation	PG Resident
Affiliation	Christian Medical College
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Fax	
Email	namithabj@gmail.com

Source of Monetary or Material Support

Source of Monetary or Material Support
> Institutional Fluid Research Grant, Office Of Research, Christian Medical College,Vellore,Tamil Nadu,pin - 632004

Primary Sponsor

Primary Sponsor Details	
Name	Christian Medical College Vellore
Address	Christian Medical College, Vellore, Tamil Nadu, India. PIN - 632004
Type of Sponsor	Research institution and hospital

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

List of Countries
India

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
Namitha B J	Christian Medical College Hospital, Vellore	General Surgery Operating Rooms,Main Operation Theatre Complex,Christian Medical College Hospital, Vellore Vellore TAMIL NADU	9880723253 namithabj@gmail.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Ethics Committee Silver, CMC Vellore	Approved	20/03/2017	No

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	colorectal cancer

Intervention / Comparator Agent

Type	Name	Details
Intervention	Lidocaine	Administered intravenously as 2mg/kg bolus followed by infusion at 2mg/kg/hr from the start of surgery till 30 minutes after surgery
Comparator Agent	Thoracic Epidural Analgesia	Thoracic Epidural Catheter is inserted at T8-T9 level through which 0.25% Bupivacaine with 1mcg/cc Fentanyl is administered as an infusion for 48 hours post operatively

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	80.00 Year(s)
Gender	Both
Details	All adult patients undergoing Laparoscopic Anterior Resections/ Ultra Low Anterior Resections/ Low Anterior Resections/ Sigmoid colectomy

	ASA I, II Patients giving consent for trial

Exclusion Criteria

Exclusion Criteria	
Details	Patient not given consent ASA 3 & 4 Electrolyte disturbances Allergy to local anaesthetic Seizure disorder Chronic opioid treatments Conversion to laparotomy

Method of Generating Random Sequence	Permuted block randomization, variable
Method of Concealment	Sequentially numbered, sealed, opaque envelopes
Blinding/Masking	Not Applicable

Primary Outcome

Outcome	Timepoints
Postoperative pain score at various intervals using Visual Analogue Score(VAS)	2,4,8,12,24 hours post operative

Secondary Outcome

Outcome	Timepoints
Quality of recovery using QoR 15 score Use of intravenous rescue analgesia (total opiods used) Length of hospital stay Side effects - with Lidocaine and Thoracic Epidural.	Quality of Recovery score 24 - 48 hours after surgery.

Target Sample Size	**Total Sample Size**=50 **Sample Size from India**=50
Phase of Trial	N/A
Date of First Enrollment (India)	27/03/2017
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years**=1 **Months**=8 **Days**=0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Open to Recruitment
Publication Details	NA
Brief Summary	Context : Postoperative pain is still a major barrier in effective recovery of the patient in any surgery. While laparoscopic pain has relatively less pain compared to open surgery, there is significant pain in the early post operative period, especially first 24 hours.

Aim :

In this study we aim to compare for patients undergoing Laparoscopic Anterior Resection/ Ultra low/ Low Anterior Resection/ Sigmoid Colectomy the effectiveness of intravenous Lidocaine and Thoracic Epidural Analgesia at attenuation of postoperative pain , the length of hospital stay and the Quality of Recovery (QoR15) score.

Study design:

Prospective, Randomized, Controlled study

Materials and methods:

After obtaining approval from Institutional Ethics Committee and written informed consent, 50 consecutive general surgical patients undergoing Laparoscopic Anterior Resection/ Low Anterior Resection/ Ultra Low Anterior Resection for carcinomatous/non carcinomatous colonic lesions will be enrolled in the study. Patients will be randomized to one of the two arms based on computer generated random numbers. Preoperatively in the ward, they will be assessed for baseline recovery parameters using QoR15 score. Patients in group A will receive intravenous Lidocaine with 2mg/kg bolus at induction followed by 2mg/kg/hr infusion till 30 minutes after surgery in Postoperative Recovery Room.

Patients assigned to the control Group B (n = 25) will have Thoracic Epidural Catheter inserted before Induction of general anaesthesia in either eighth or ninth thoracic intervertebral space. A bolus of 3 - 5 ml of 0.25% Bupivacaine will be given, followed by an infusion at 5-8ml/hr for the next 48 hrs to provide bilateral segmental sensory block between T7 and L3 dermatomes.

Systolic, diastolic, mean blood pressure and heart rate, saturation will be recorded at baseline, post intubation, post extubation in the recovery. Thereafter, haemodynamic parameters will be recorded every 30 minutes till patient is discharged to the ward. Intraoperative total analgesic (fentanyl, paracetamol, tramadol, NSAIDS) use will be noted. Post operative pain will be assessed using Visual analogue Pain Intensity Rating score at 2, 4, 8, 12 and 24 hours post operatively. The patient recovery characteristics will be recorded using the QoR 15 score between 24 - 48 hours post operative. All patients will receive intravenous Fentanyl 10-20 mcg with a lockout period of 15 minutes through patient controlled drug delivery system (CADD Pump) for 24 hours postoperative.

ANNEXURE – 7 – DATA (EXCEL)

slno	name	hospno	age	gender	asa	weight	height	bmi	group	surgerywe	sugery	htn	dm	cardio	allergies	asthma	hypothy	hyperthy	prsurgery	allergie
1	Mst.Rahil	748063g	49	2	1	60	152	26	1	2		0	0	0	0	0	0	0	0	
2	Mohiyudh	745640g	54	1	2	89	180	27.5	1	2		1	0	0	0	0	0	0	0	
3	Beebi K	811110g	67	2	2	74	144	35.7	1	1		1	0	0	0	0	1	0	0	
4																				
5	Faruk Ahn	752866g	42	1	1	65	164	24.1	1	3		0	0	0	0	0	0	0	1	
6	Sivam.G	442517f	66	1	2	63	164	23.4	2	2		0	1	0	1	0	0	0	1	
7	Elizabeth	895225g	56	2	2	65	161	25.1	2	1		0	0	0	0	0	1	0	0	
8	Nirmal Da	751951g	49	1	2	71	156	29.2	1	2		1	1	0	0	0	0	0	0	
9	Sharmin A	075539h	24	2	1	75	160	29	1	3		0	0	0	0	0	0	0	1	
10																				
11	Sathyamo	974116b	37	1	1	66	175	21.6	1	3		0	0	0	0	0	0	0	0	
12	Anju Naid	871911g	48	2	2	54	152	23.4	2	4		0	0	0	0	0	1	0	0	
13	Jaker Hos	723985g	29	1	1	56	171	19.2	2	2		0	0	0	0	0	0	0	0	
14	Matthew.	811092g	68	1	2	85	176	27.4	1	2		1	0	0	0	0	0	0	1	
15	Deivasiga	976585g	66	1	2	55	172	18.6	2	1		0	0	0	0	0	0	0	0	
16	Jahangir A	869958g	31	1	1	65	165	23.9	1	3		0	0	0	0	0	0	0	0	
17	Ouseph	875997g	63	1	2	68	174	22.5	1	3		0	0	0	0	0	0	0	0	
18	Md.Abdul	832088g	60	1	1	60	167	21.5	2	3		0	0	0	0	0	0	0	0	
19	TML.Sush	567381g	66	2	2	61	156	27.1	2	2		1	0	0	0	0	0	0	0	
20	Alok Kum	906049g	55	1	2	65	166	23.6	2	2		1	0	0	1	0	0	0	0	
21	Anadi Cha	086225h	63	1	1	58	165	21.3	1	1		0	0	0	0	0	0	0	0	
22	Laili Akter	966073g	22	2	1	47	155	19.6	1	2		0	0	0	0	0	0	0	0	
23	Jahangir A	982119g	45	1	1	59	160	23	1	2		0	0	0	0	0	0	0	0	
24	Mahmuda	917391g	39	1	1	57	157	23.1	2	2		0	0	0	0	0	0	0	1	
25	Partha Mc	966885g	31	1	1	77	173	25.7	2	1		0	0	0	0	0	0	0	0	
26	Salma Beg	871803g	26	2	1	51	142	25.3	1	2		0	0	0	0	0	0	0	1	
27	Md.Mohir	109510h	35	1	1	52	154	21.9	1	1		0	0	0	0	0	0	0	1	
28	Lizzy	036847h	62	2	2	77	155	32	1	1		0	0	0	0	0	0	0	0	
29	Sura Begu	157668h	45	2	1	62	150	27.5	2	1		0	0	0	0	0	0	0	0	
30	Deepak Th	099267h	60	1	2	61	160	23.8	2	4		1	0	0	0	0	0	0	0	
31	Md.Abdul	164138h	60	1	2	64	164	23.8	1	1		1	1	0	0	0	0	0	0	
32	Md.Dalwa	171508h	56	1	2	57	168	20.9	2	1		1	1	0	0	0	0	0	0	
33	Mankaj Ku	988573g	40	1	1	89	176	27.1	1	3		0	0	0	0	0	0	0	0	
34	Md.Abdul	178349h	59	1	2	60	175	19.6	2	2		1	0	0	0	0	0	0	0	
35	Alhaz Md.	095681h	70	1	2	67	170	23.3	1	2		1	0	0	0	0	0	0	1	
36	John Geor	193178h	35	1	1	58	166	21	2	2		0	0	0	0	0	0	0	0	
37	Savina R M	270434h	47	2	1	60	154	25.4	2	4		0	0	0	0	0	0	0	0	

	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO
1	allergies1	ponv	motion	chronic	fentanyl	morphine	parace	nsaids	tramadol	crystal	colloid	blood	bldloss	totalfluid	surgery	anaest	lidocaine	thoracic	extubat	pulsebase	pulsep
2	0	0	0	0	160	0	1	0	0	1.2	0	0	100	1200	230	285	300	0	10	69	
3	0	0	0	0	200	0	1	0	0	1.5	0	0	300	1500	315	375	405		15	79	
4	0	0	0	0	300	3	1	0	0	1.5	0	0	100	1500	240	330	360		15	79	
5																					
6	0	0	0	0	100		1			0.7			100	700	220	260			20	73	
7	1	0	0	0	160		1			1.4			150	1400	330	420			15	98	1
8	0	0	0	0	100		1				1		150	1000	160	260			15	68	
9	0	0	0	0	200	3	1	75		1			200	1000	240	285	315		5	82	
10	0	0	0	0	240		1		50	2	0.5		150	2500	375	410	440		20	101	
11																					
12	0	0	0	0	300	10	1	75	50	1.5			150	1500	320	360	390		10	80	
13	0	0	0	0	200	4	1			1			100	1	240	310			15	88	
14	0	0	0	0	270	5	1			2			200	2000	255	285			10	88	
15	0	0	0	0	180	5	2			1.7			200	1700	435	480	510		15	77	
16	0	0	0	0	180		1			1	0.5		100	1500	165	210			10	71	
17	0	0	0	0	200	5	1			1			100	1000	210	255	285		10	85	
18	0	0	0	0	120		1			1			190	1000	300	360	390		15	64	
19	0	0	0	0	100		1			1.5			150	1500	210	270			15	79	
20	0	0	0	0	250		1			2			150	2000	225	340			20	64	
21	1	0	0	0	170	3	1			2			100	2000	300	360			10	92	
22	0	0	0	0	160	3	1			1			100	1000	220	270	300		15	85	
23	0	0	0	0	210		1			1			40	1000	240	280	310		10	106	
24	0	0	0	0	200		1		100	2.5			200	2500	320	400	430		30	90	
25	0	0	0	0	150	8	1	50		2			200	2000	350	460			20	97	

	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN
26	0	0	0	0	200	3	1			1.5			100	1500	240	300			15	101
27	0	0	0	0	200		1			1.5			100	1500	300	360	390		15	100
28	0	0	0	0	260	2	1	50		2.2			100	2200	330	360	390		20	89
29	0	0	0	0	200		1			1.5			100	1500	300	360	390		9	90
30	0	0	0	0	160		1			1			100	1000	180	230			10	90
31	0	0	0	0	140	6	1			1.5			100	1500	190	225			7	82
32	0	0	0	0	220		1			0.5	0.2		100	700	130	180	210		8	77
33	0	0	0	0	200		1			0.8			100	800	160	225			12	92
34	0	0	0	0	200		1	75		2			150	2000	390	465	495		14	80
35	0	0	0	0	200		1			2.7			200	2700	280	320			20	90
36	0	0	0	0	300		1		100	2	0.5		200	2500	225	300	330		20	94
37	0	0	0	0	300		1		100	1.5	0.5		250	2000	360	390			16	96
38	0	0	0	0	160		1			1.5			50	1500	105	180			15	78

	AO	AP	AQ	AR	AS	AT	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
1	pulsepost	pulse5m	pulse30m	pulse1hr	pulse15hr	pulse2hr	sbpbase	sbppost	sbp5m	sbp30m	sbp1hr	sbp15hr	sbp2hr	dbpbase	dbppost	dbp5m	dbp30m	dbp1hr	dbp15hr	dbp2hr
2	72	71	72	78	76	80	126	75	128	125	120	122	128	74	54	68	66	60	68	69
3	66	96	85	65	66	72	137	97	128	132	137	147	142	78	71	64	52	72	61	62
4	63	62	60	62	62	68	158	111	148	137	142	144	140	77	73	72	71	82	84	80
5																				
6	76	67	70	69	64	63	110	114	103	100	100	105	108	73	70	75	58	58	60	61
7	100	91	93	102	100	98	143	138	140	162	170	158	146	80	87	84	92	90	90	86
8	62	72	62	60	60	64	146	94	100	118	114	122	121	86	54	54	65	64	61	60
9	75	78	75	84	84	82	151	119	137	148	159	144	138	90	80	82	83	85	86	82
10	80	113	111	92	119	112	122	100	132	123	123	122	120	70	58	80	72	88	78	80
11																				
12	90	82	78	90	100	88	107	94	116	115	130	137	131	69	65	50	57	66	66	61
13	72	76	65	82	80	72	157	92	115	136	130	130	124	92	61	72	64	62	80	74
14	76	90	92	84	87	90	124	92	132	140	130	134	130	76	60	92	91	90	90	88
15	68	92	72	80	82	80	134	102	106	132	130	124	126	75	70	74	71	74	70	72
16	59	74	72	80	78	74	131	61	122	117	112	109	110	98	47	86	72	74	72	76
17	72	75	76	76	75	80	129	100	130	139	137	132	130	85	60	68	66	72	70	66
18	64	76	74	66	68	70	110	84	120	121	124	126	122	70	44	68	66	71	70	70
19	68	55	63	75	69	66	134	104	154	150	147	140	135	79	62	80	79	81	80	80
20	60	58	61	63	62	66	138	110	115	113	110	108	114	75	60	63	60	60	62	64
21	83	94	97	101	98	94	130	120	138	126	149	136	130	82	80	86	87	93	90	88
22	87	83	82	93	100	90	124	74	137	115	129	111	112	77	48	80	71	86	69	70
23	80	100	80	88	86	86	115	106	100	94	105	122	113	76	70	54	65	76	82	72
24	63	95	76	82	76	87	124	80	119	120	139	139	133	84	52	89	80	87	83	93
25	74	81	78	80	76	82	124	106	135	132	110	100	118	81	68	100	86	70	70	72

	AO	AP	AQ	AR	AS	AT	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
26	79	100	96	93	90	91	118	83	122	122	118	116	120	84	56	79	72	77	70	74
27	84	96	100	102	100	100	130	100	126	123	120	112	112	97	70	75	70	70	72	70
28	95	98	91	94	93	90	130	102	140	146	149	151	138	79	70	69	80	83	81	80
29	91	74	71	69	80	82	140	121	145	143	139	151	128	80	78	93	93	89	96	85
30	80	90	86	90	95	92	108	98	126	116	115	114	115	68	64	71	69	62	60	73
31	61	82	80	78	80	79	148	86	150	140	142	134	138	83	62	83	84	84	80	82
32	80	72	63	63	65	68	190	141	171	176	162	160	162	88	79	87	87	92	90	93
33	100	86	86	93	90	87	120	100	140	141	119	117	120	80	78	90	91	90	87	90
34	72	70	74	72	74	72	116	108	114	140	114	140	145	92	80	90	80	92	86	80
35	91	78	74	68	69	74	150	100	138	128	128	114	129	83	63	82	84	74	69	69
36	68	97	100	98	105	95	122	70	127	124	128	124	122	74	40	68	75	77	73	72
37	80	75	72	94	77	80	122	100	114	128	132	130	128	70	58	70	75	80	77	75
38	74	57	62	64	66	68	125	101	175	173	176	160	164	78	63	96	93	96	89	92

	BI	BJ	BK	BL	BM	BN	BO	BP	BQ	BR	BS	BT	BU	BV	BW	BX	BY	BZ	CA	CB
1	mapbase	mappost	map5m	map30m	map1hr	map15hr	map2hr	sp02base	spo2post	sp025m	sp0230m	sp021hr	sp0215hr	sp022hr	rrbase	rrpost	rr5m	rr30m	rr1hr	rr15hr
2	88	62	83	79	72	86	89	100	100	99	94	95	97	98	14	16	16	20	20	18
3	98	80	85	79	94	90	89	100	100	100	100	100	100	100	12	12	16	17	15	16
4	104	86	97	93	102	104	100	100	100	100	98	99	99	100	14	14	14	16	18	16
5																				
6	85	85	84	72	72	75	77	98	100	100	95	95	96	96	20	15	36	28	22	20
7	101	104	103	115	117	113	106	98	100	100	100	100	100	98	18	12	17	17	14	15
8	106	65	69	83	81	81	80	100	100	100	100	100	98	98	18	12	16	16	16	18
9	110	93	100	105	110	105	101	100	100	100	100	100	100	100	15	14	14	18	18	18
10	87	72	97	89	100	93	93	100	100	100	100	100	100	100	15	12	16	14	13	18
11																				
12	82	75	72	76	87	90	84	98	100	100	100	100	100	100	20	14	22	20	20	20
13	114	71	86	88	85	97	91	100	100	100	100	99	99	99	15	14	18	16	18	20
14	92	71	105	107	103	105	102	100	100	100	100	99	99	99	17	12	14	16	20	22
15	95	81	85	91	93	88	90	97	100	100	99	99	99	98	14	12	22	19	20	21
16	109	52	98	87	87	84	87	99	96	100	100	100	100	100	17	14	18	20	20	21
17	100	73	89	90	94	91	87	100	100	100	100	100	100	100	22	14	20	16	20	18
18	83	57	85	84	89	89	87	100	100	94	98	100	100	100	14	15	22	22	24	24
19	97	76	105	103	103	100	98	99	100	100	100	96	96	96	15	14	15	14	16	18
20	96	77	80	78	77	77	81	98	100	100	100	100	100	100	12	14	14	16	15	13
21	98	93	103	100	112	105	102	100	100	100	99	99	99	99	22	14	24	22	24	22
22	93	57	99	86	100	83	84	100	100	100	100	100	100	100	16	12	18	20	24	24
23	89	82	69	75	86	95	86	100	100	100	100	100	100	100	13	12	12	16	14	15
24	97	61	99	93	104	102	106	100	100	99	100	100	100	100	14	13	16	18	22	20
25	95	81	112	101	83	80	87	100	100	100	100	100	100	100	20	12	18	20	17	19

	BI	BJ	BK	BL	BM	BN	BO	BP	BQ	BR	BS	BT	BU	BV	BW	BX	BY	BZ	CA	CB
26	95	65	93	89	91	85	89	99	100	99	100	98	98	98	12	12	14	16	20	18
27	108	80	92	88	87	85	84	100	100	100	100	99	99	98	18	14	18	20	20	20
28	96	81	93	102	105	104	99	99	100	100	98	97	96	97	14	12	15	15	16	16
29	100	92	110	110	106	114	99	95	100	100	100	100	100	100	18	14	16	20	18	16
30	81	75	89	85	80	78	87	100	100	100	100	100	100	100	14	12	16	16	16	16
31	105	70	105	103	103	98	101	99	100	100	100	100	100	100	16	12	14	12	13	14
32	122	100	115	117	115	113	116	100	100	100	100	100	100	100	14	12	22	24	24	22
33	93	85	107	108	100	97	100	100	100	100	100	100	100	100	15	12	22	22	22	20
34	100	89	98	100	99	104	102	100	100	93	96	96	99	99	16	12	17	16	16	20
35	108	75	101	99	92	84	89	99	100	100	100	100	97	98	14	11	16	18	16	18
36	90	50	88	91	94	90	89	97	100	100	100	98	98	98	14	12	14	18	20	22
37	87	72	85	93	97	95	93	100	100	100	100	100	99	99	16	12	12	14	14	15
38	94	76	122	120	123	113	116	97	100	100	100	100	96	96	14	14	15	16	16	14

	CC	CD	CE	CF	CG	CH	CI	CJ	CK	CL	CM	CN	CO	CP	CQ	CR	CS	CT	CU	CV
1	n2hr	painbase	pain5m	pain30m	pain1hr	pain15hr	pain2hr	drug	time	dose	numbness	dizziness	tinnitus	confusion	nausea	tremors	convul	cardiac	hypot	urinary
2	20	0	0	4	0	4	5				0	0	0	0	0	0	0	0		
3	19	0	4	5	5	5	5				0	0	0	0	0	0	0	0		
4	18	2	5	6	7	7	8	2	90	30	0	0	0	0	0	0	0	0		
5																				
6	21	0	0	2	3	3	3				0	0	0	0	0	0	0	0		
7	18	0	3	3	4	4	4												0	1
8	20	0	0	2	2	3	3												0	0
9	16	5	1	2	2	1	1				0	0	0	0	0	0	0	0		
10	20	0	4	2	2	0	0				0	0	0	0	0	0	0	0		
11																				
12	20	1	2	2	4	4	4				0	0	0	0	0	0	0	0		
13	20	0	0	1	1	1	1												0	0
14	18	2	2	4	4	4	4												0	0
15	22	2	0	0	0	1	1				0	0	0	0	0	0	0	0		
16	20	5	1	0	0	0	1												0	0
17	21	2	5	2	2	0	0	2	5	30	0	0	0	0	0	0	0	0		
18	22	0	0	0	0	2	2				0	0	0	0	0	0	0	0		
19	17	0	0	0	0	0	0												0	0
20	14	0	0	0	0	0	0												1	0
21	24	0	0	0	0	0	0												0	0
22	22	3	0	0	0	0	0				0	0	0	0	0	0	0	1		
23	16	0	0	0	2	2	2				0	0	0	0	0	0	0	0		
24	22	0	0	6	8	7	7	2	90	3	0	0	0	0	0	0	0	0		
25	20	0	7	7	5	5	5	2	5	8									0	0

	CC	CD	CE	CF	CG	CH	CI	CJ	CK	CL	CM	CN	CO	CP	CQ	CR	CS	CT	CU	CV
26	20	0	0	0	0	2	2												0	0
27	18	0	5	6	8	7	7	1	30	75	0	0	0	0	1	0	0	0		
28	18	0	0	0	5	5	5				0	0	0	0	0	0	0	0		
29	18	2	7	7	7	8	6	2	120	6	0	0	0	0	0	0	0	0		
30	16	0	0	0	2	2	0				0	0	0	0	0	0	0	0	0	0
31	12	0	0	0	0	2	2												0	0
32	23	0	0	0	0	2	2				0	0	0	0	0	0	0	0		
33	21	0	0	0	0	2	2												0	0
34	22	0	2	2	4	4	4				0	0	0	0	0	0	0	0		
35	16	0	0	0	8	2	2	2	60	20									0	0
36	22	3	0	0	2	2	4				0	0	0	0	1	0	0	0		
37	18	3	0	0	0	2	4												0	0
38	14	3	5	7	7	6	6	2	5	40									0	0

	CW	CX	CY	CZ	DA	DB	DC	DD	DE	DF	DG	DH	DI	DJ	DK	DL	DM	DN	DO	DP
1	catheter	unilate	numbness	inadeanal	analgesia	motor	powpaina	powpain2	powpain4	powpain8	powpain1	powpain2	caddarr	cadd2hr	cadd4hr	cadd8hr	cadd12hr	cadd24hr	rescue	time1
2							4	6	5	4	2	2	2	8	15	17	22	25		
3							8	6	3	3	4	3	6	8	14	22	29	29		
4							9	9	9	5	4	4	2	3	5	8	8	16	morphine	2
5																				
6							3	3	4	2	2	2	1	2	2	7	10	17		
7	0	0	0	0	t5 - t12	5	4	6	2	1	1	1	1	2	2	3	4	4		
8	0	1	0	0	T5 - L1	5	3	6	5	4	5	3	0	2	4	5	8	8		
9							1	5	3	3	2	1	0	4	6	6	7	8		
10							0	6	4	4	4	4	0	2	3	3	4	6		
11																				
12							4	2	1	1	2	2	4	7	10	11	16	16		
13	0	0			T4 - L1	5	1	0	0	0	0	0	1	1	1	1	1	1		
14	0	0	0	0	T5 - L1	5	2	4	2	0	0	0	3	4	4	4	4	4		
15							1	1	2	2	2	2	0	1	5	6	8	12		
16	0	0	0	0	T5 - L1	5	4	4	4	0	1	1	2	5	9	14	14	15		
17							0	4	5	3	3	2	2	7	12	20	24	28		
18							0	2	0	0	2	0	1	4	6	7	10	12		
19	0	0	0	0	T5 - L1	5	1	0	0	0	0	2	1	1	2	2	2	3		
20	0	0	0	1	T4 - T12	5	0	0	0	3	3	5	6	2	0	1	1	4	Epidural B	3
21	1	0	0	0	no level	5	0	0	0	0	0	1	0	0	0	0	0	2		
22							0	2	8	2	7	6	2	8	14	18	19	21		
23							2	4	2	6	4	4	1	4	8	14	23	35		
24							5	4	4	4	3	3	4	9	14	20	23	30		
25	0	0	0	1	T4 - T10	5	5	6	5	5	4	4							Morphine	48

	CW	CX	CY	CZ	DA	DB	DC	DD	DE	DF	DG	DH	DI	DJ	DK	DL	DM	DN	DO	DP
26	0	0	0	0	T4 - T12	5	2	4	4	2	2	2	3	7	13	18	18	20		
27							8	8	8	8	7	7	4	9	14	18	28	32	Morphine	12
28							7	4	2	2	2	2	2	6	12	12	17	21		
29							4	2	2	1	0	2	6	11	18	20	23	26		
30	0	0	0	0	T4 - L2(at T	5	2	2	4	4	2	2	4	8	12	20	27	30		
31	1	0	0	0	NO LEVEL	5	3	2	2	0	0	0	2	3	5	7	10	13		
32							3	2	3	2	2	3	1	2	3	4	5	6		
33	1	0	0	0	T3 - L1	5	2	2	0	1	1	1	1	2	3	6	7	10		
34							8	8	6	6	6	4	3	5	7	10	16	21		
35	0	0			T3 - T12	5	2	2	4	2	2	1	2	4	5	7	13	19		
36							5	5	5	4	2	2	6	11	15	20	26	32		
37	0	0	0	0	T4-L1	5	5	5	4	2	1	1	0	1	2	3	4	6		
38	0	0	0	0	T3 - L1	5	8	7	3	3	4	4	4	10	11	11	12	15		

	DQ	DR	DS	DT	DU	DV	DW	DX	DY	DZ	EA	EB	EC	ED	EE	EF	EG	EH	EI	EJ
1	discharge	breathe	food	rested	goodsleep	toilet	family	doctors	home	comfort	wellbeing	moderate	severe	nausea1	anxious	feelsad	preopscr	breathe1	food1	rested1
2	5	10	10	10	10	10	10	10	10	9	10	10	10	10	10	10	149	10	10	10
3	6	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	148	10	10	7
4	6	10	9	5	9	10	10	10	10	10	9	8	10	10	5	8	143	10	5	10
5																				
6	39	10	10	10	9	10	10	10	10	10	10	10	10	10	5	8	142	8	4	5
7	14	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	7	4	9
8	7	10	10	10	10	10	10	10	10	10	10	10	10	10	9	10	149	10	5	7
9	7	10	10	10	10	10	10	10	10	10	10	5	9	10	10	10	144	10	7	7
10	5	10	10	10	10	8	10	10	8	9	9	10	10	10	10	10	144	10	10	8
11																				
12	17	10	10	10	10	10	10	10	10	10	10	9	10	10	9	10	148	10	10	10
13	6	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	10	10
14	5	10	10	10	10	10	10	10	10	10	10	8	10	7	8	8	141	10	10	9
15	5	9	10	9	9	10	10	10	10	10	10	8	10	10	8	9	142	9	8	8
16	11	10	10	10	10	10	10	10	10	10	10	5	10	10	10	10	145	10	9	9
17	4	10	10	10	10	10	10	10	10	10	10	8	10	10	8	10	146	7	10	8
18	8	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	149	10	9	10
19	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	149	5	9	9
20	6	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	2	8
21	8	10	10	10	9	10	10	10	10	10	10	10	10	10	10	10	149	10	4	10
22	5	10	10	10	10	10	10	10	9	10	10	7	10	10	10	10	146	10	10	10
23	7	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	10	9
24	12	10	10	7	8	10	10	10	8	10	10	10	10	10	10	10	143	10	2	5
25	11	10	8	9	10	10	10	10	10	10	10	10	10	10	5	7	139	9	5	8

	DQ	DR	DS	DT	DU	DV	DW	DX	DY	DZ	EA	EB	EC	ED	EE	EF	EG	EH	EI	EJ
26	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	5	10
27	10	10	10	10	10	10	10	10	10	10	6	10	10	10	6	5	137	10	10	9
28	5	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	9	10
29	6	10	9	10	9	9	10	10	9	10	10	9	10	10	9	9	143	10	8	9
30	7	10	10	9	8	10	10	10	9	9	8	10	10	6	8	8	135	10	9	9
31	4	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	10	10
32	6	10	10	4	4	8	10	9	7	4	5	8	10	10	3	2	104	10	10	4
33	4	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	8	10
34	14	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	150	10	8	6
35		10	5	8	5	10	10	10	10	9	9	8	10	10	10	10	134	10	5	8
36	10	7	9	7	8	7	9	10	7	8	8	7	10	10	9	10	126	7	1	3
37	18	10	6	5	3	10	10	10	10	10	9	6	4	10	4	5	112	9	4	4
38	6	10	10	7	7	10	10	10	10	8	8	6	10	10	8	7	131	10	8	7

	EK	EL	EM	EN	EO	EP	EQ	ER	ES	ET	EU	EV	EW	EX	EY
1	goodsleep	toilet1	family1	doctors1	home1	comfort1	wellbeing	moderate	severe1	nausea2	anxious1	feelsad1	postopscr	timeqor	postopcour
2	10	10	10	10	10	10	10	5	10	10	10	10	145	30	
3	10	10	10	10	10	10	10	8	9	9	10	10	143	44	
4	9	10	10	8	10	10	10	5	10	10	10	10	137	36	
5															
6	6	2	10	10	5	8	8	5	10	10	5	8	104	26	3
7	5	3	10	10	4	8	10	7	10	3	7	9	106	36	
8	6	4	10	10	9	7	8	6	10	5	10	10	117	28	
9	7	7	8	8	8	9	10	8	9	10	10	10	128	32	3
10	10	8	10	10	8	8	9	8	10	10	10	10	139	48	
11															
12	9	10	10	10	3	10	10	4	5	1	2	10	114	48	2
13	10	10	10	10	10	10	10	10	10	10	10	10	150	30	
14	8	8	10	10	8	9	8	8	10	10	8	8	134	36	
15	8	9	10	10	10	10	10	8	10	10	9	9	138	36	
16	7	7	8	7	7	8	6	8	10	10	8	9	123	46	1
17	10	10	10	10	10	10	10	8	10	10	10	10	143	31	
18	9	9	10	10	7	10	10	10	10	10	10	10	144	30	3
19	6	9	10	10	6	8	8	8	10	5	9	9	121	36	
20	8	2	2	10	2	6	6	6	10	6	9	9	96	42	
21	9	10	10	10	9	9	10	9	10	5	8	8	121	36	3
22	8	10	10	10	7	7	7	7	10	10	10	10	136	34	
23	10	9	10	10	8	10	8	6	10	2	9	9	130	48	
24	8	6	10	10	5	5	5	6	10	4	5	7	98	48	3
25	9	1	9	4	1	8	8	2	1	5	8	9	87	48	

	EK	EL	EM	EN	EO	EP	EQ	ER	ES	ET	EU	EV	EW	EX	EY
26	5	5	10	10	8	10	10	8	10	10	10	10	131	30	
27	10	8	10	10	5	7	7	2	5	10	5	5	113		
28	10	10	10	10	10	10	10	9	10	10	10	10	148	36	
29	9	9	10	10	8	8	8	7	10	10	8	9	133	33	
30	8	9	10	10	10	9	10	8	10	2	9	10	133	34	
31	9	10	10	10	9	10	10	8	10	10	10	10	146	36	
32	8	8	10	10	7	4	5	7	10	10	4	5	112	42	
33	10	10	10	10	10	7	8	8	10	10	10	10	141	32	
34	5	2	9	10	3	7	7	7	4	10	8	10	106	38	3
35	10	8	10	10	7	7	9	8	10	10	9	9	130	40	3
36	3	5	7	10	2	4	3	3	3	4	4	4	63	40	3
37	4	2	8	10	3	3	5	7	10	1	5	5	80	32	2
38	9	8	10	10	8	7	8	5	10	8	8	7	123	48	

ANNEXURE – 8 – ABBREVIATIONS AND OTHERS

ASA – American Society of Anaesthesiologists

AR – Anterior Resection

LAR – Low Anterior Resection

UL – LAR – Ultra Low Anterior Resection

SC – Sigmoid Colectomy

BMI – Body Mass Index

CTRI – Clinical Trials Registry - India

CADD – Continuous Ambulatory Drug Delivery

ERAS – Enhanced Recovery After Surgery

ED 50 – Effective Dose, for 50% of people receiving the drug

PCA – Patient Controlled Analgesia

IRB – Institutional Review Board

IUPAC – International Union of Pure and Applied Chemistry

MEAC – Minimum Effective Analgesic Concentration

NSAIDS – Non Steroidal Anti – Inflammatory Drugs

NRS – Numerical Rating Scale

PONV – Postoperative Nausea and Vomiting

QoR - 15 – Quality of Recovery 15 Questionnaire

SBP – Systolic Blood Pressure

SEER – Surveillance, Epidemiology and End Results program

TEA – Thoracic Epidural Analgesia

DBP – Diastolic Blood Pressure

MAP – Mean Arterial Pressure

PACU – Post Anaesthesia Care Unit

SD – Standard Deviation

SPSS – Statistical Package for the Social Sciences

WHO – World Health Organization

LIST OF TABLES

LIST OF FIGURES